Use of tyrosine kinase inhibitors for treating cerebral ischemia

The present invention relates to a method for treating cerebral ischemia, comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cells degranulation to a human in need of such treatment. Such compounds can be chosen from tyrosine kinase inhibitors and more particularly non-toxic, selective and potent c-kit inhibitors. Preferably, said inhibitor is unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

The most common clinical causes of hypoxic-ischemic encephalopathy are stroke, traumatic brain injury such as cerebral edema and thromboembolic occlusions of cerebral arteries. This results in a drop in cerebral perfusion, hypoxia and hypoglycemia, ultimately leading to selective or global neuronal loss. The outcome of cerebral ischemia will depend on several factors such as the area concerned and the duration of the brain energy shortage. For example, in major ischemic insults, all cortical neurons and glial cells may be affected and damages may extend to the brainstem. Brain death is deemed to occur when loss of cerebral and brainstem function is observed.

Furthermore, following reperfusion, additional injury to the cells occurs with the production of free radicals and lactic acid, the formation of cerebral edema and the development of inflammation.

Patient surviving an episode of cerebral ischemia may nevertheless be afflicted with irremediable consequences including memory loss, attention, and/or perception loss, emotional disorders, social behavioral problems, paralysis, aphasia, and posttraumatic

epilepsy. In this regards, it has been estimated that about half of stroke victims experience mild to severe disability which lead to impaired life style and quality as well as increased health related costs.

Tissue plasminogen activator is used to reopen occluded vessels, but it must be administered within three hours of cerebral injury. As mentioned above, reperfusion involves a release of metabolites and inflammatory compounds which induces a secondary nerve cells destruction process.

Other treatments may be initiated within 24-hour post-trauma and may positively affect the outcome. However, the efficacy of antioxidant such as Tirilazad® and other compounds such as phenytoin, phenobarbital, carbamazepine or valproate for preventing the onset of post-traumatic syndromes has not been demonstrated as of today. Thyroid hormones have been proposed in US 5,571,840 for the treatment of cerebral ischemia following cardiac arrest. However, these hormones have numerous detrimental side-effects. In US 5,827,832, citicoline is proposed to be administered shortly after an ischemic episode and thereafter as an intermediate in the biosynthesis of membrane phosphatidyl choline, which is involved in cellular integrity. The general purpose of using such compound is to promote protection of nerve cells following reperfusion.

Therefore, there is still a great need for improved methods of treating or preventing the damages resulting from cerebral ischemia, and more particularly a method of obviating the secondary destruction process which is inherent to reperfusion.

Postischemic cerebral inflammation has been reported to contribute to ischemic brain damage with significant increase in the number of mast cells (MC) in the hypophysis (Dropp et al, Acta Anat (Basel) 1979;105(4):505-13). Mast cell tryptase activates PAR2

(protease-activated receptors). Proteolytic activation of PARs is irreversible, and coupled to signalling cascades involved in 'emergency situations', such as trauma and inflammation (Cottrell et al, Essays Biochem 2002;38:169-83).

In addition, an elevation of histamine level was seen in basal ganglia following experimental infarction in monkeys due to proliferation of mast cells (Subramanian et al, J Neural Transm 1981;50(2-4):225-32). Histamine causes consistent blood-brain barrier opening (Abbott et al, Cell Mol Neurobiol 2000 Apr;20(2):131-47). The release of histamine from mast cells at the ischemic site play a central role in microvascular permeability and arteriolar constriction that might aggravate cerebral oedema. It is assumed that excessive release of histamine leads to the activation of H2-receptor-coupled adenylate cyclase in the brain microvessels and to the induction of brain edema (Sztriha et al, Neurosci Lett 1987 Apr 10;75(3):334-8). Histamine also potentiates NMDA receptor-mediated excitotoxicity in conditions where enhanced glutamatergic neurotransmission is observed in conjunction with tissue acidification, such as cerebral ischaemia. On the other hand, it was observed that rapid intestinal ischaemia-reperfusion injury is suppressed in genetically mast cell-deficient Ws/Ws rats (Andoh A. et al, 2001;63 Suppl 1:103-7).

In connection with the present invention, we propose here that Mast cells (MC) are central players involved in neuronal death and particularly in apoptosis induced by brain trauma, cerebrovascular ischemia and ischemic conditions. The inflammation process during reperfusion attracts mast cells to the site of injury which in turn sustain more damages. Liberation by activated mast cells of mediators contributes to the biochemical cascades that participate in neuronal death and particularly in apoptosis induced by brain trauma.

Indeed, following mast cells activation, released granules liberate various factors which directly or indirectly participate in the destruction of neurons. A cocktail of different proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes) and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN-γ) further increase the inflammation and destruction process.

To prevent such additional damages, the present invention proposes to deplete mast cells using compounds that are substantially specific to mast cells. In this regard, tyrosine kinase inhibitors and more particularly c-kit specific kinase inhibitors are proposed to inhibit mast cell proliferation, survival and activation.

A new route for treating cerebral ischemia and related disorders is provided, which consists of destroying mast cells involved in and contributing to the nerve cells death.

It has been found that tyrosine kinase inhibitors and more particularly c-kit inhibitors are especially suited to reach this goal.

Description

The present invention relates to a method for treating ischemia, more particularly cerebral ischemia, comprising administering a compound capable of depleting mast cells or a compound inhibiting mast cells degranulation to a human in need of such treatment.

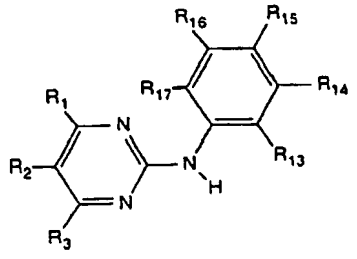
Said method for preventing or treating ischemia can comprise administering a tyrosine kinase inhibitor, preferably a c-kit inhibitor, to a human in need of such treatment.

Preferred compounds are c-kit inhibitors, more particularly a non-toxic, selective and potent c-kit inhibitors. Such inhibitors can be selected from the group consisting of 2-(3-

amino)arylamino-4-aryl-thiazoles, pyrimidine derivatives, pyrrolopyrimidine derivatives, quinazoline derivatives, quinoxaline derivatives, pyrazoles derivatives, bis monocyclic, bicyclic or heterocyclic aryl compounds, vinylene-azaindole derivatives and pyridyl-quinolones derivatives, styryl compounds, styryl-substituted pyridyl compounds, seleoindoles, selenides, tricyclic polyhydroxylic compounds and benzylphosphonic acid compounds.

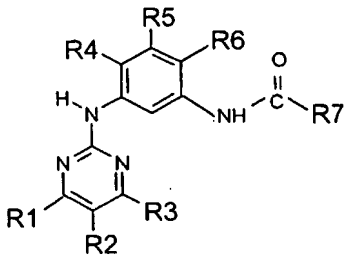
Among preferred compounds, it is of interest to focus on pyrimidine derivatives such as N-phenyl-2-pyrimidine-amine derivatives (US 5,521,184 and WO 99/03854), indolinone derivatives and pyrrol-substituted indolinones (US 5,792,783, EP 934 931, US 5,834,504), US 5,883,116, US 5,883,113, US 5, 886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, US 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, US 3,772,295 and US 4,343,940), 4-amino-substituted quinazolines (US 3,470,182), 4-thienyl-2-(1H)-quinazolones, 6,7-dialkoxyquinazolines (US 3,800,039), aryl and heteroaryl quinazoline (US 5,721,237, US 5,714,493, US 5,710,158 and WO 95/15758), 4-anilinoquinazoline compounds (US 4,464,375), and 4-thienyl-2-(1H)-quinazolones (US 3,551,427).

So, preferably, the invention relates to a method for treating cerebral ischemia comprising administering a non toxic, potent and selective c-kit inhibitor is a pyrimidine derivatives, more particularly N-phenyl-2-pyrimidine-amine derivatives of formula I :



wherein the R1, R2, R3, R13 to R17 groups have the meanings depicted in EP 564 409 B1, incorporated herein in the description.

Preferably, the N-phenyl-2-pyrimidine-amine derivative is selected from the compounds corresponding to formula II :

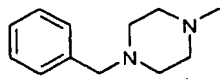


Wherein R1, R2 and R3 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl or a cyclic or heterocyclic group, especially a pyridyl group;

R4, R5 and R6 are independently chosen from H, F, Cl, Br, I, a C1-C5 alkyl, especially a methyl group;

and R7 is a phenyl group bearing at least one substituent, which in turn possesses at least one basic site, such as an amino function.

Preferably, R7 is the following group :



Among these compounds, the preferred are defined as follows :

R1 is a heterocyclic group, especially a pyridyl group,

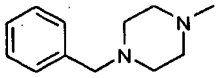
R2 and R3 are H,

R4 is a C1-C3 alkyl, especially a methyl group,

R5 and R6 are H,

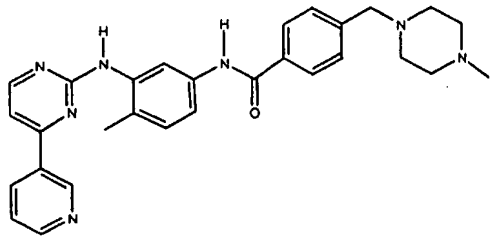
and R7 is a phenyl group bearing at least one substituent, which in turn possesses at least one

basic site, such as an amino function, for example the group :



Therefore, in a preferred embodiment, the invention relates to a method for preventing or treating ischemia, more particularly cerabral ischemia, comprising the administration of an effective amount of the compound known in the art as CGP57148B :

4-(4-méhylpipérazine-1-ylméthyl)-N-[4-méthyl-3-(4-pyridine-3-yl)pyrimidine-2 ylamino)phényl]-benzamide corresponding to the following formula :

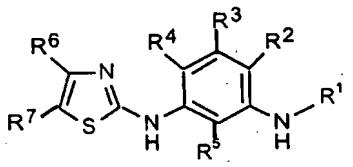


The preparation of this compound is described in example 21 of EP 564 409 and the β-form, which is particularly useful is described in WO 99/03854.

Alternatively, the c-kit inhibitor can be selected from :

- indolinone derivatives, more particularly pyrrol-substituted indolinones,
- monocyclic, bicyclic aryl and heteroaryl compounds, quinazoline derivatives,
- and quinaxolines, such as 2-phényl-quinaxoline derivatives, for example 2-phenyl-6,7-dimethoxy quinaxoline.

In another preferred embodiment, the invention contemplated the method mentioned above, wherein said c-kit inhibitor is selected from 2-(3-amino)arylamino-4-aryl-thiazoles such as those chosen from formula III for which the applicant filed US 60/400064 :



FORMULA III

and wherein R^1 is :

a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

c) a -CO-NH-R, –CO-R, -CO-OR or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,

iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

and R^7 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

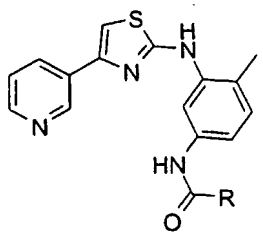
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any

combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

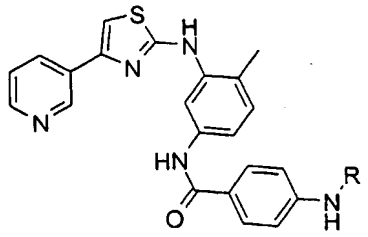
iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

In another preferred embodiment, when R^1 has the meaning depicted in c) above, the invention is directed to compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality.

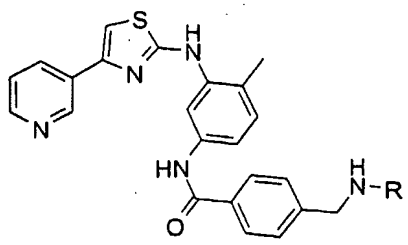
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to **amide-aniline** compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality;

a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

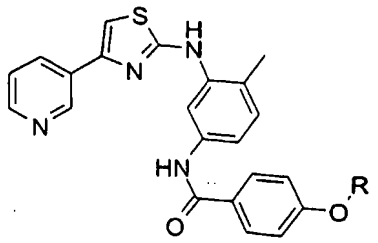
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to **amide-benzylamine** compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to **amide-phenol** compounds of the following formula:

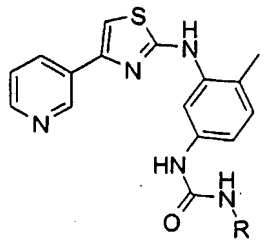


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality;

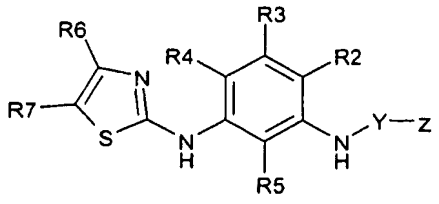
a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to **urea** compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following formula:



wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms;

wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more ring position with any permutation of the following groups:

- a halogen such as F, Cl, Br, I;
- a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an O-R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an NRaRb, where Ra and Rb represents a hydrogen, or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality or a cycle; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a

cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an NHCOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group

substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an NHCONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;
- an OSO_2R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally

substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an $NRaOSO_2Rb$, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

and R^7 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

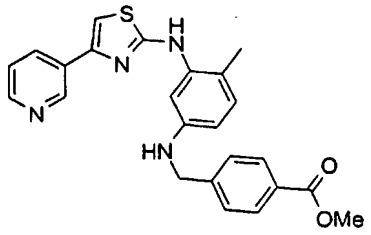
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

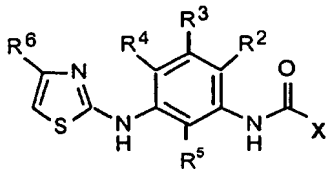
iv) H, an halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

An example of preferred compounds of the above formula is depicted below:

001 : 4-{[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester



Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula IV :



FORMULA IV

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl , or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

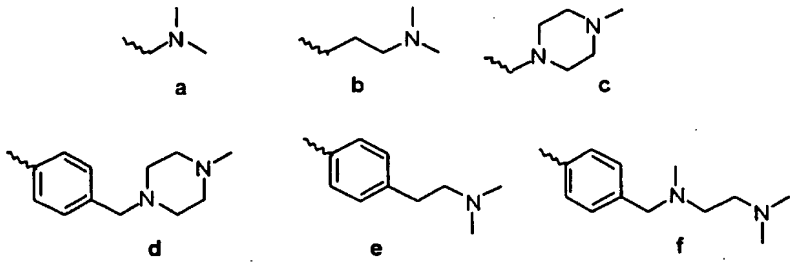
(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

In another alternative, substituent R6, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

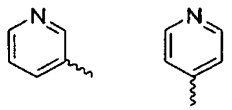
Among the preferred compounds corresponding formula IV, the invention is directed to compounds in which X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures **a** to **f** shown

below, wherein the wavy line corresponds to the point of attachment to core structure of formula **IV**:



Among group **a** to **f**, X (see formula II) is preferentially group **d.**

Furthermore, among the preferred compounds of formula **III** or **IV**, the invention concerns the compounds in which R^2 and R^3 are hydrogen. Preferentially, R^4 is a methyl group and R^5 is H. In addition, R^6 is preferentially a 3-pyridyl group (cf. structure g below), or a 4-pyridyl group (cf. structure h below). The wavy line in structure g and h correspond to the point of attachment to the core structure of formula **III or IV**.



Thus, the invention contemplates:

1- A compound of formula IV as depicted above, wherein X is group **d** and R^6 is a 3-pyridyl group.

2- A compound of formula IV as depicted above, wherein X is group **d** and R^4 is a methyl group.

3- A compound of formula III or IV as depicted above, wherein R^1 is group **d** and R^2 is H.

4- A compound of formula III or IV as depicted above, wherein R^1 is group **d** and R^3 is H.

5- A compound of formula III or IV as depicted above, wherein R^1 is group **d** and R^2 and/or R^3 and/or R^5 is H.

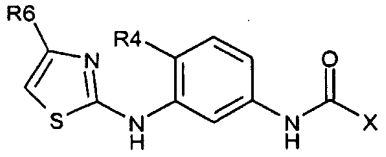
6- A compound of formula III or IV as depicted above, wherein R^6 is a 3-pyridyl group and R^3 is a methyl group.

7- A compound of formula III or IV as depicted above, wherein R^6 is a 3-pyridyl group and R^2 is H.

8- A compound of formula III or IV as depicted above, wherein R^2 and/or R^3 and/or R^5 is H and R^4 is a methyl group.

9- A compound of formula III or IV as depicted above wherein R^2 and/or R^3 and/or R^5 is H, R^4 is a methyl group and R^6 is a 3-pyridyl group.

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein R2, R3, R5 are hydrogen, corresponding to the following formula IV-1 :



FORMULA IV-1

wherein X is R or NRR' and wherein R and R' are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom

or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

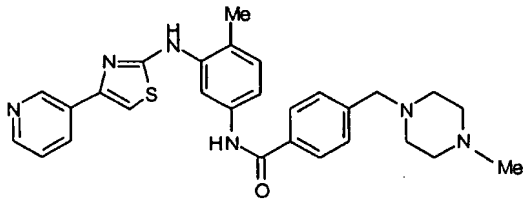
iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and

optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

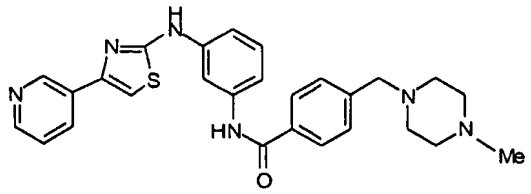
In another alternative, substituent R6, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

Examples :

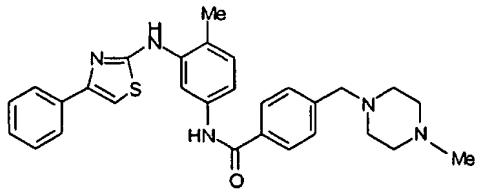
002 : 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole



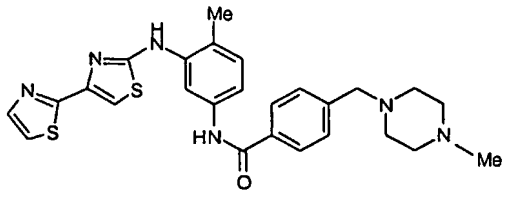
003 : 4-(4-Methyl-piperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



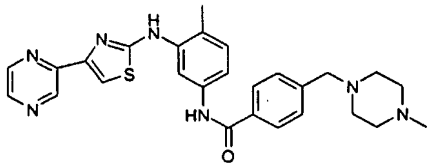
004 : N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



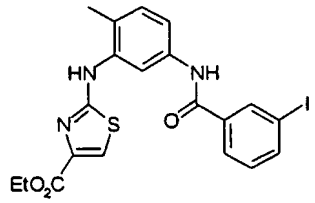
005 : N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



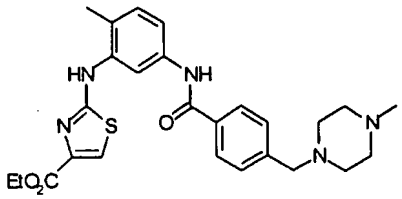
006 : 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrazin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



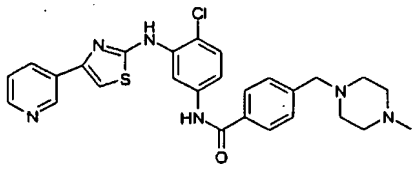
007: 2-[5-(3-Iodo-benzoylamino)-2-methyl-phenylamino]-thiazole-4-carboxylic acid ethyl ester



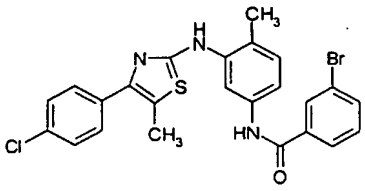
008: 2-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-benzoylamino]-phenylamino}-thiazole-4-carboxylic acid ethyl ester



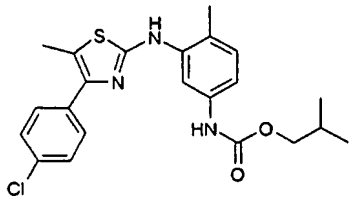
027 : 2-(2-chloro-5-amino)phenyl-4-(3-pyridyl)-thiazole



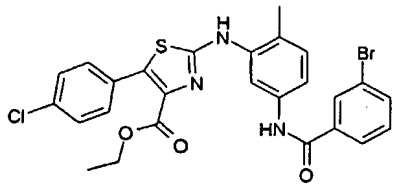
128: 3-Bromo-N-{3-[4-(4-chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-benzamide



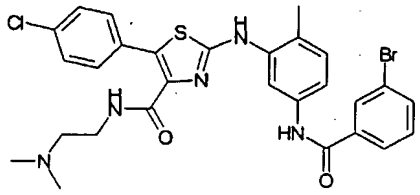
129: {3-[4-(4-Chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-carbamic acid isobutyl ester



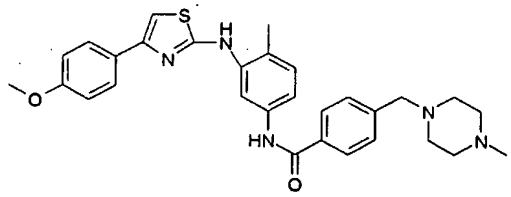
130: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid ethyl ester



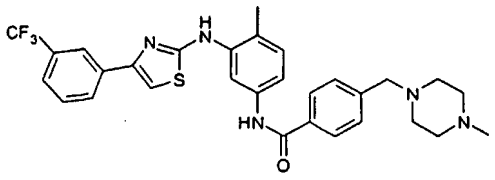
131: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid (2-dimethylamino-ethyl)-amide



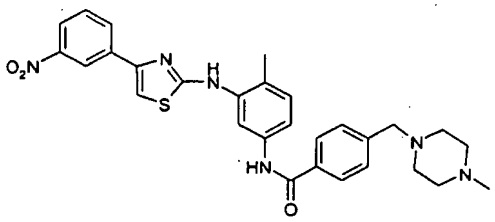
110: N-{3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1 ylmethyl)-benzamide



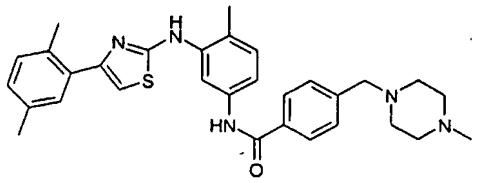
116: 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl}-benzamide



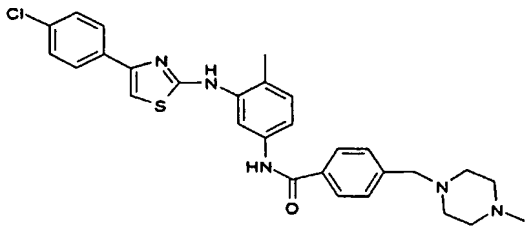
117 : N-{4-Methyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



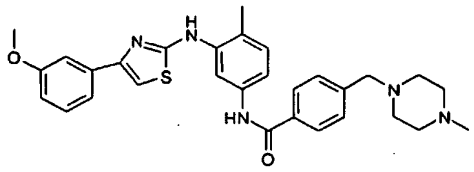
124 : N-{3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



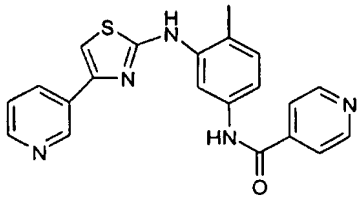
108: N-{3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



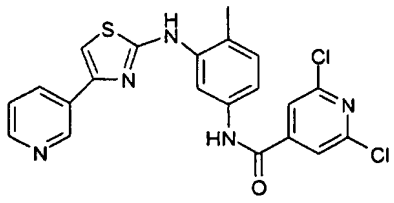
113: N-{3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



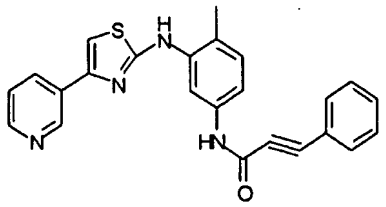
063: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



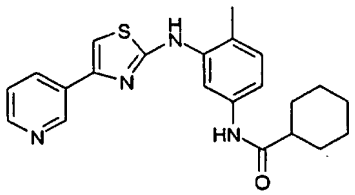
064: 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



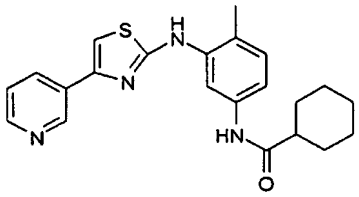
091: 3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



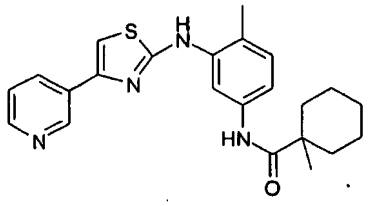
092: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide



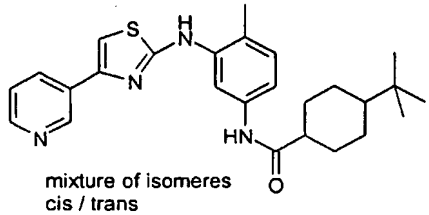
093: 5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester



094: 1-Methyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide

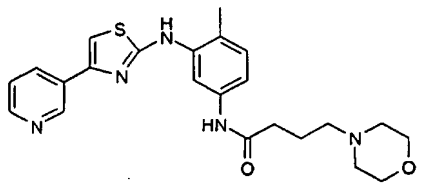


095: 4-tert-Butyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



mixture of isomeres
cis / trans

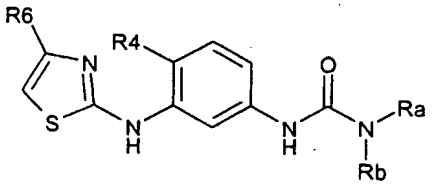
096: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-yl-butyramide



beige powder mp : 116-120°C

^{1}H RMN (DMSO-d^6) δ = 1.80-2.00 (m, 2H) ; 2.29 (s, 3H) ; 2.30-2.45 (m, 6H) ; 3.55-3.65 (m, 6H) ; 7.15-7.25 (m, 2H) ; 7.46-7.50 (m, 2H) ; 7.52 (s, 1H) ; 8.35 (d, J = 6.2 Hz, 1H) ; 8.55 (dd, J = 1.5 Hz, J = 4.7 Hz, 2H) ; 9.22 (s, 1H) ; 9.45 (s, 1H) ; 9.93 (s, 1H)

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a urea group, a -CO-NRR' group, corresponding to the [3-(thiazol-2-ylamino)-phenyl]-urea family and the following formula IV-2 :



FORMULA IV-2

wherein Ra, Rb are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

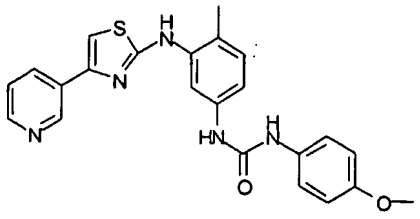
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

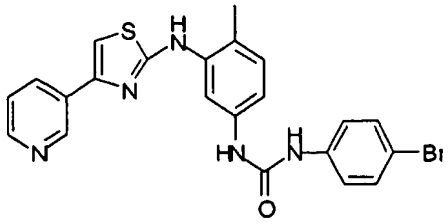
iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Examples

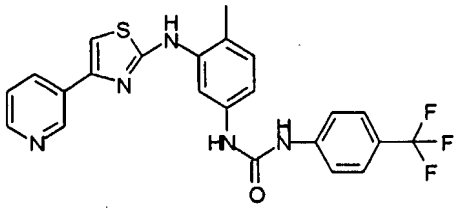
009: 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



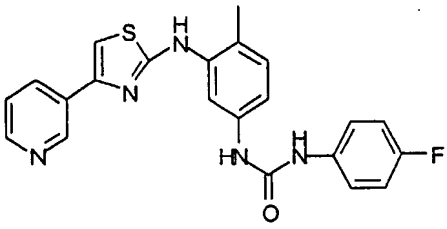
010: 1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



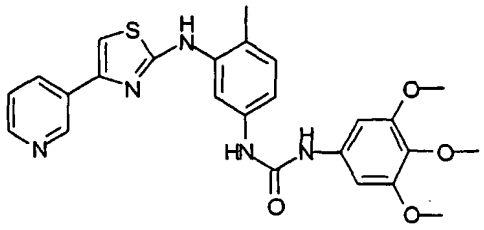
011: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea



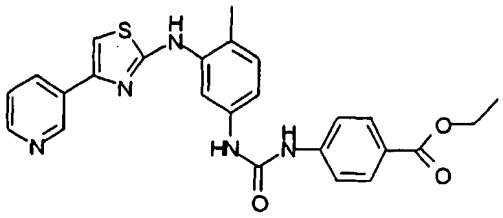
012: 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



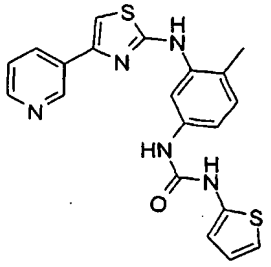
013: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea



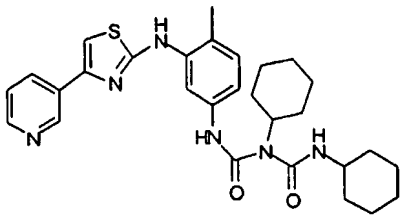
014: 4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester



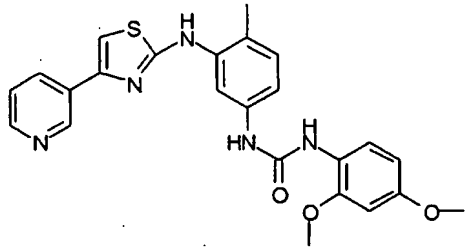
015: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea



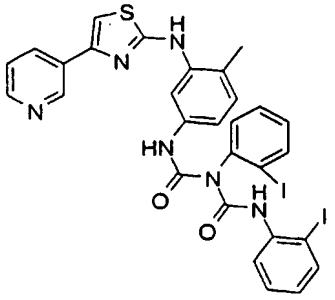
016: 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



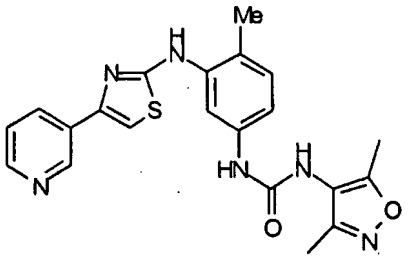
017: 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



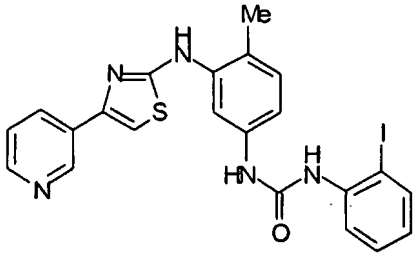
018: 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



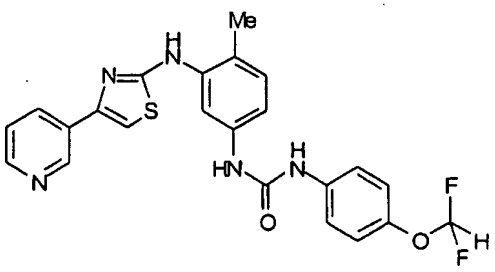
019: 1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



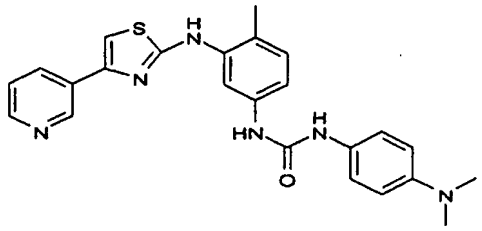
020: 1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



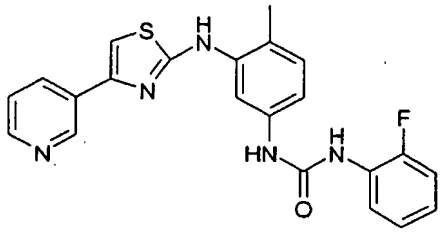
021: 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



022: 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



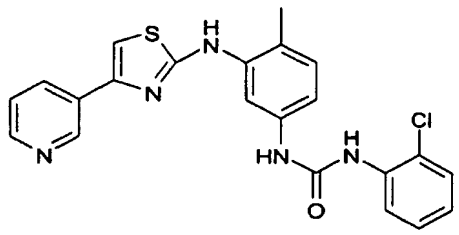
023: 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



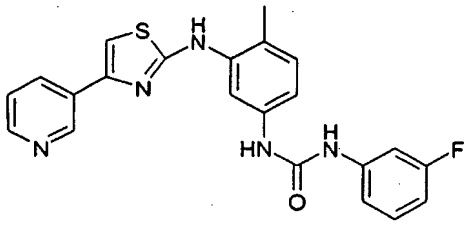
light brown powder mp : 203-206°C

^{1}H NMR (DMSO-d^6) : δ= 2.24 (s, 3H) ; 6.98-7.00 (m, 2H) ; 7.10-7.23 (m, 3H) ; 7.40 (m, 1H) ; 7.48 (s, 1H) ; 8.25 (m, 1H) ; 8.37 (d, J = 7.8 Hz, 1H) ; 8.51 (m, 3H) ; 9.03 (s, 1H) ; 9.19 (s, 1H) ; 9.39 (s, 1H)

024: 1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



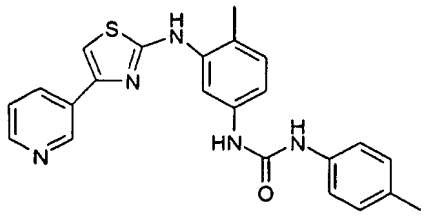
025: 1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



white powder mp : 210-215°C

^{1}H NMR (DMSO-d^6) : δ = 2.24 (s, 3H) ; 6.79 (t, J = 6.3 Hz, 1H) ; 6.99 (m, 1H) ; 7.09-7.14 (m, 2H) ; 7.30 (m, 1H) ; 7.41 (t, J = 4.7 Hz, 1H) ; 7.48 (s, 1H) ; 7.56 (d, J = 1.2 Hz, 1H) ; 8.39 (d, J = 8.0 Hz, 1H) ; 8.49-8.52 (m, 2H) ; 8.71 (s, 1H) ; 8.87 (s, 1H) ; 9.18 (s, 1H) ; 9.38 (s, 1H)

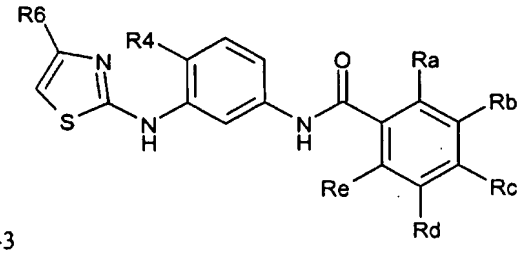
026: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea



white powder mp : 238-240°C

^{1}H RMN (DMSO-d^6) δ = 2.29 (s, 3H) ; 2.31 (s, 3H) ; 7.05 (d, J = 6.2 Hz, 1H) ; 7.10-1.16 (m, 3H) ; 7.42-7.49 (m, 3H) ; 7.53 (s, 1H) ; 8.35-8.62 (m, 5H) ; 9.22 (d, J = 1.6 Hz, 1H) ; 9.43 (s, 1H)

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a -substituted Aryl group, corresponding to the N-[3-(Thiazol-2-ylamino)-phenyl]-amide family and the following formula IV-3 :



FORMULA IV-3

wherein Ra, Rb, Rc, Rd, Re are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and

R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and or bearing a pendant basic nitrogen functionality;

Ra, Rb, Rc, Rd, Re may also be

- a halogen such as I, Cl, Br and F

- a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a -SO2-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or

heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an OSO_2R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an $NRaOSO_2Rb$, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- a CN group

- a trifluoromethyl group

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

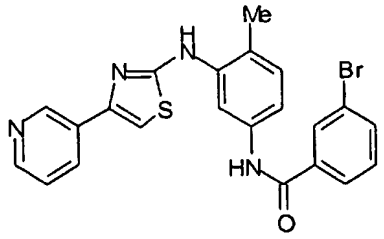
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

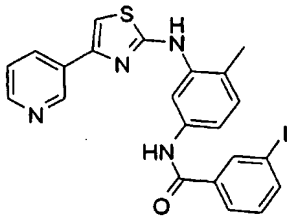
iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Examples

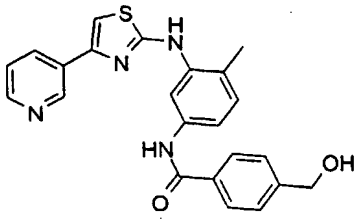
028: 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



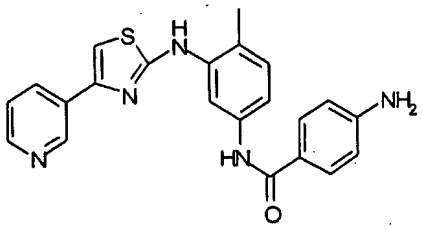
029: 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



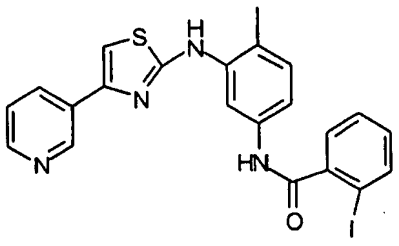
030: 4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



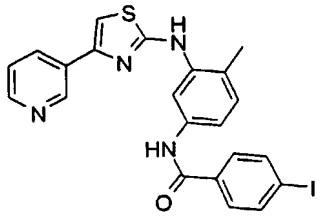
031: 4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



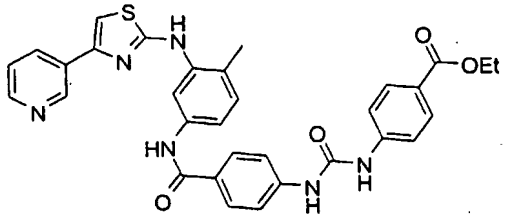
032: 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



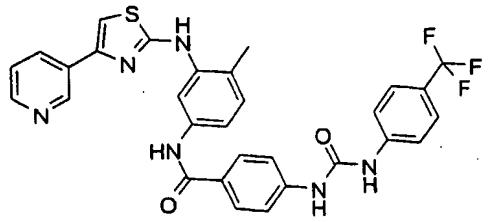
033: 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



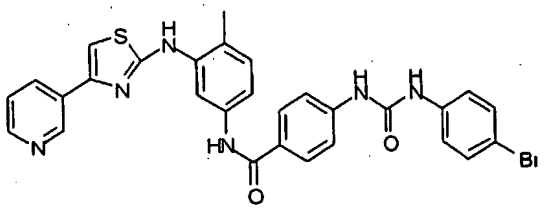
034: 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester



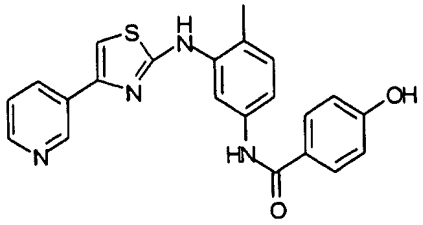
035: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide



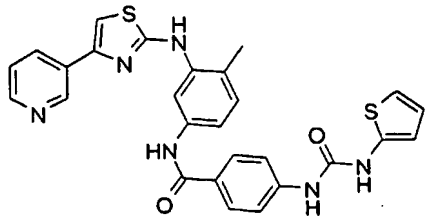
036: 4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



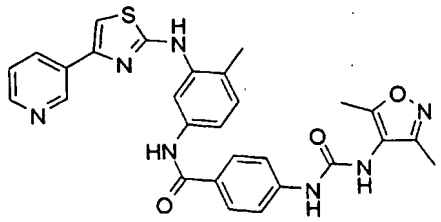
037: 4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



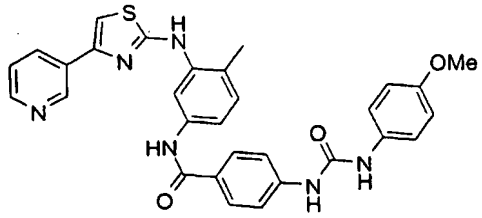
038: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide



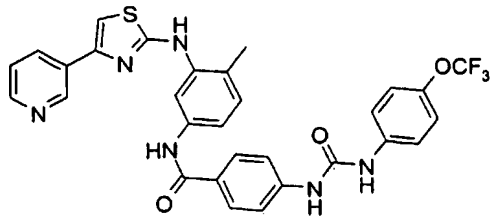
039: 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



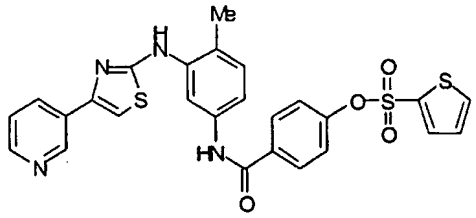
040: 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



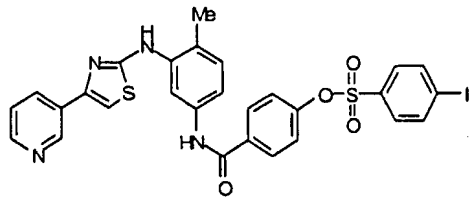
041: 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



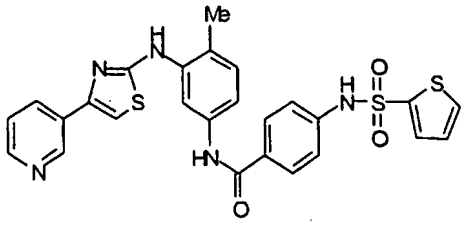
042: Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



043: 4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



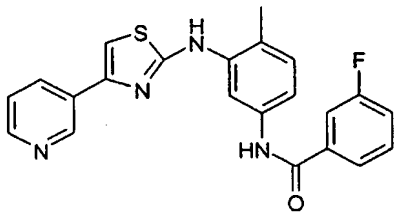
044: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(thiophene-2-sulfonylamino)-benzamide



brown powder mp : 230-233°C

^{1}H NMR (DMSO-d^6) δ = 2.29 (s, 3H) ; 7.15-7.18 (m, 2H) ; 7.22-7.32 (m, 3H) ; 7.48 (m, 2H) ; 7.67 (dd, J = 1.3 Hz, J = 3.7 Hz, 1H) ; 7.90-7.96 (m, 3H) ; 8.38-8.42 (m, 1H) ; 8.51 (m, 1H) ; 8.57 (d, J = 1.9 Hz, 1H) ; 9.17 (d, J = 1.7 Hz, 1H) ; 9.44 (s, 1H) ; 10.12 (s, 1H) ; 10.82 (s, 1H)

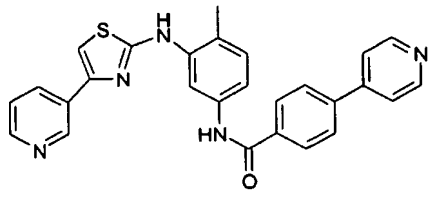
045: 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



off-white foam mp : 184-186°C

^{1}H NMR (CD_3OD-d^4) : δ = 2.23 (s, 3H) ; 7.12-7.14 (m, 2H) ; 7.20-7.23 (m, 2H) ; 7.30 (m, 1H) ; 7.43 (m, 1H) ; 7.50 (m, 1H) ; 7.66 (d, J = 1.0 Hz, 1H) ; 8.23 (m, 1H) ; 8.33 (m, 1H) ; 8.38 (s, 1H) ; 8.98 (s, 1H)

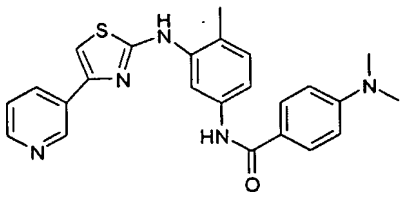
046: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide



yellow powder mp : 254-256°C

^{1}H NMR (DMSO-d^6) : δ 2.34 (s, 3H) ; 7.28 (d, J = 8.0 Hz, 1H) ; 7.45-7.49 (m, 2H) ; 7.54 (s, 1H) ; 7.78 (t, J = 7.6 Hz, 1H) ; 7.89-7.91 (m, 2H) ; 8.10 (t, J = 7.8 Hz, 2H) ; 8.37-8.42 (m, 2H) ; 8.55 (d, J = 4.7 Hz, 1H) ; 8.73-8.77 (m, 3H) ; 9.24 (s, 1H) ; 9.52 (s, 1H) ; 10.43 (s, 1H)

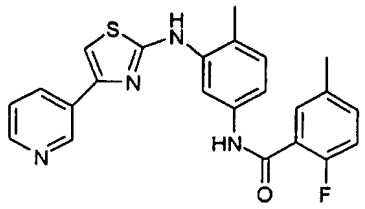
047: 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp : 147-150°C

^{1}H NMR (DMSO-d^6) : δ 2.25 (s, 3H) ; 2.99 (s, 6H) ; 6.76 (d, J = 8.9 Hz, 2H) ; 7.16 (d, J = 8.3 Hz, 1H) ; 7.35 (d, J = 2.0 Hz, 1H) ; 7.44-7.47 (m, 2H) ; 7.86-7.89 (m, 2H) ; 8.34-8.36 (m, 1H) ; 8.48-8.50 (m, 1H) ; 8.56-8.57 (m, 1H) ; 9.16 (s, 1H) ; 9.44 (s, 1H) ; 9.85 (s, 1H)

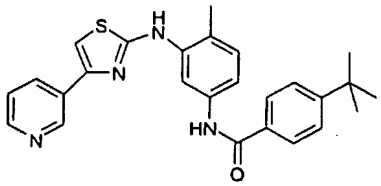
048: 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown orange powder mp : 103-106°C

^{1}H RMN (DMSO-d^6) δ = 2.26 (s, 3H) ; 2.35 (s, 3H) ; 7.17-7.47 (m, 7H) ; 8.29 (dd, J = 1.6 Hz, J = 7.9 Hz, 1H) ; 8.47 (d, J= 3.5 Hz, 1H) ; 8.57 (s, 1H) ; 9.15 (d, J = 2.0 Hz, 1H) ; 9.44 (s, 1H) ; 10.33 (s, 1H)

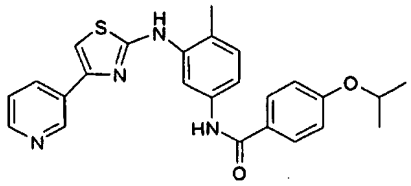
049: 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown powder mp : 145-150°C

^{1}H RMN (DMSO-d^6) δ = 1.32 (s, 9H) ; 2.04 (s, 3H) ; 7.18 (d, J = 8.4 Hz, 1H) ; 7.35-7.44 (m, 2H) ; 7.46 (s, 1H) ; 7.55 (d, J = 8.5 Hz, 1H) ; 7.90 (d, J = 8.5 Hz, 1H) ; 8.32 (d, J = 7.9 Hz, 1H) ; 8.47 (dd, J = 1.5 Hz, J = 4.7 Hz, 1H) ; 8.60 (d, J = 2.0 Hz, 1H) ; 9.15 (d, J = 1.7 Hz, 1H) ; 9.43 (s, 1H) ; 10.15 (s, 1H)

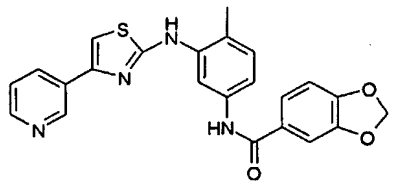
050: 4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



brown powder mp : 154-155°C

^{1}H RMN (DMSO-d^6) δ = 1.34 (d, J = 5.9 Hz, 6H) ; 4.72 (hept, J = 5.9 Hz, 1H) ; 7.01 (d, J = 7.0 Hz, 2H) ; 7.18 (d, J = 8.5 Hz, 1H) ; 7.35-7.44 (m, 2H) ; 7.46 (s, 1H) ; 7.94 (dd, J = 2.0 Hz, J = 6.7 Hz, 2H) ; 8.32 (d, J = 8.3 Hz, 1H) ; 8.48 (dd, J = 3.3 Hz, J = 4.8 Hz, 1H) ; 8.58 (d, J = 2.0 Hz, 1H) ; 9.15 (d, J = 1.8 Hz, 1H) ; 9.43 (s, 1H) ; 10.4 (s, 1H)

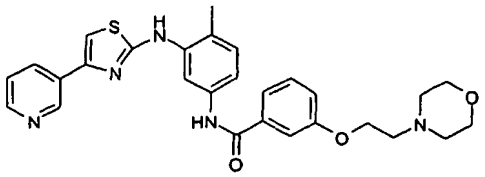
051: Benzo[1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-amide



brown orange powder mp : 130-132°C

^{1}H RMN (DMSO-d^6) δ = 2.23 (s, 3H) ; 6.10 (s, 2H) ; 7.03 (d, J = 8.1 Hz, 1H) ; 7.15 (d, J = 8.3 Hz, 1H) ; 7.25-7.55 (m, 6H) ; 8.26 (s, 1H) ; 8.45 (dd, J = 1.5 Hz, J = 4.7, 1H) ; 8.55 (d, J = 2.0 Hz, 1H) ; 9.12 (d, J = 1.7 Hz, 1H) ; 9.40 (s, 1H) ; 10.01 (s, 1H)

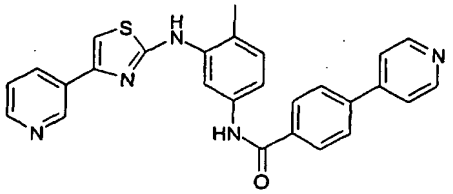
052: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide



beige yellow powder mp : 75-80°C

^{1}H RMN (DMSO-d^6) δ = 2.10-2.25 (m, 4H) ; 2.50-2.60 (m, 2H) ; 3.19 (s, 3H) ; 3.41-3.48 (m, 4H) ; 4.00-4.06 (m, 2H) ; 7.00-7.11 (m, 2H) ; 7.22-7.35 (m, 6H), 8.18 (d, J = 8.0 Hz, 1H) ; 8.33 (d, J = 0.9 Hz, 1H) ; 8.49 (d, J = 1.7 Hz, 1H) ; 9.03 (s, 1H) ; 9.31 (s, 1H) ; 10.05 (s, 1H)

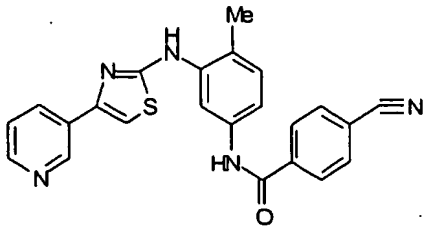
053: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-4-pyridin-4-yl-benzamide



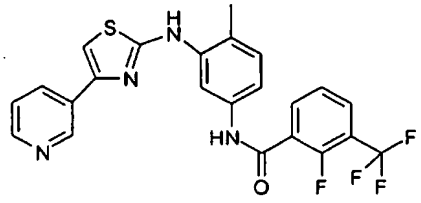
brown powder mp : dec. 250°C

^{1}H RMN (DMSO-d^6) δ = 2.28 (s, 3H) ; 7.21 (d, J = 7.9 Hz, 1H) ; 7.30-7.50 (m, 3H) ; 7.81 (d, J = 4.7 Hz, 1H) ; 7.98 (d, J = 7.5 Hz, 2H) ; 8.13 (d, J = 7.9 Hz, 2H) ; 8.32 (d, J = 7.7 Hz, 1H) ; 8.48 (d, J = 4.9 Hz, 1H) ; 8.62-8.69 (m, 3H) ; 9.16 (s, 1H) ; 9.45 (s, 1H) ; 10.34 (s, 1H)

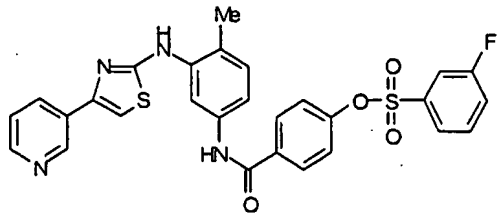
054: 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



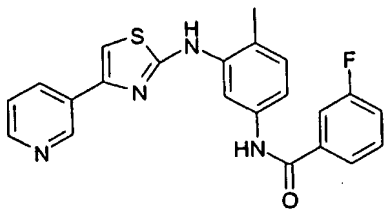
055: 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide



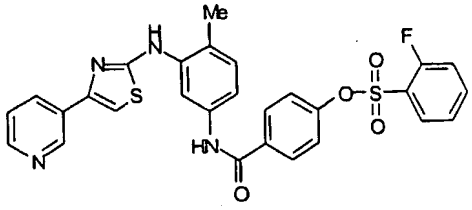
056: 3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



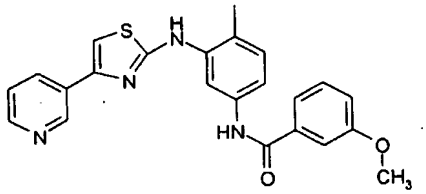
057: 4-Aminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



058: 2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



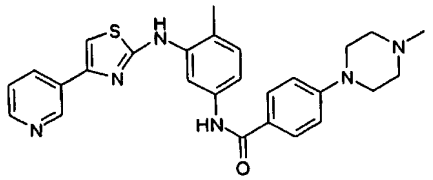
059: 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



white powder mp : 76-79°C

^{1}H RMN (DMSO-d^6) δ = 2.32 (s, 3H) ; 3.89 (s, 3H) ; 7.22-7.25 (m, 2H), 7.44-7.58 (m, 4H), 8.28-8.35 (m, 1H) ; 8.52 (dd, J = 1.6 Hz, J = 4.7 Hz, 1H) ; 8.66 (d, J = 2.0 Hz, 1H) ; 9.20 (d, J = 1.4 Hz, 1H) ; 9.50 (s, 1H) ; 10.25 (s, 1H)

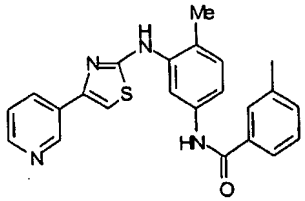
060: 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



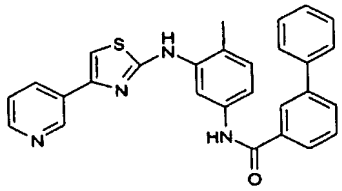
beige brown powder mp : 128-130°C

^{1}H RMN (DMSO-d^6) δ = 2.15 (s, 3H) ; 2.18 (s, 3H) ; 2.35-2.41 (m, 4H) ; 3.18-3.3.24 (m, 4H) ; 6.94 (d, J = 8.9 Hz, 2H) ; 7.09 (d, J = 8.4 Hz, 1H) ; 7.28-7.38 (m, 3H) ; 7.81 (d, J = 8.9 Hz, 2H) ; 8.20-8.25 (m, 1H) ; 8.40 (dd, J = 1.6 Hz, J = 4.7 , 1H) ; 8.48 (d, J = 1.9 Hz, 1H) ; 9.07 (d, J = 1.5 Hz, 1H) ; 9.35 (s, 1H) ; 9.84 (s, 1H)

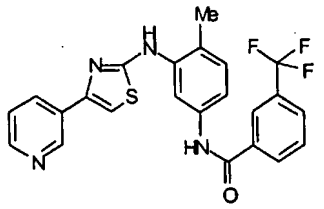
061: 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



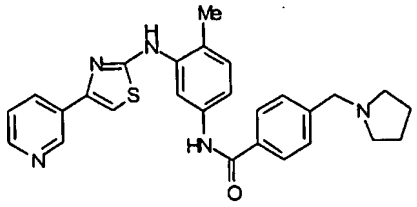
062: Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



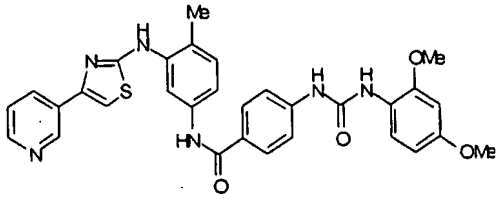
065: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide



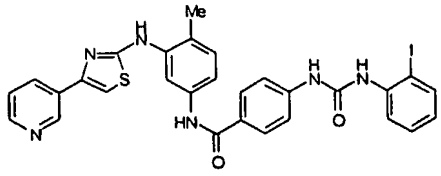
099: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide



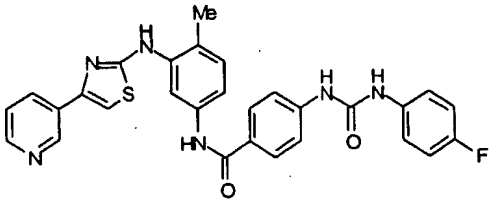
100: 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



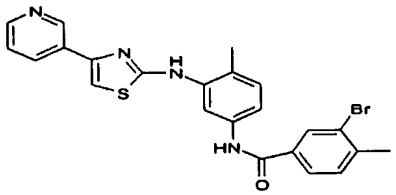
101: 4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



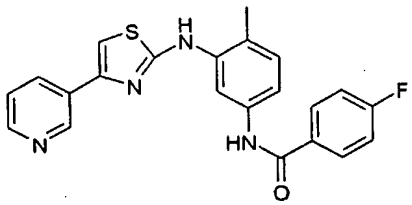
102: 4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



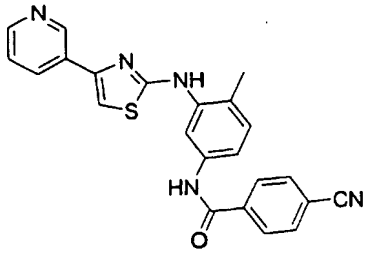
105: 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



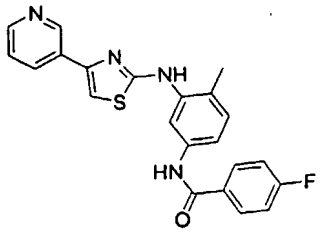
106: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



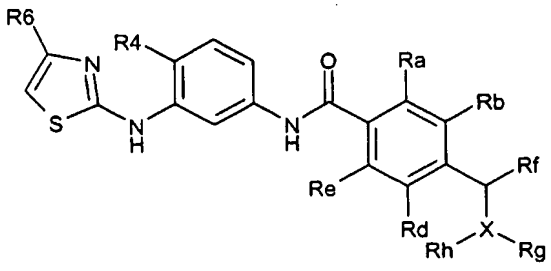
103: 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



104: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



Among compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a –substituted-aryl group, corresponding to the 4-(4-substituted-1-ylmethyl)-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula IV-4 :



FORMULA IV-4

wherein X is a heteroatom, such as O or N

wherein Ra, Rb, Rd, Re, Rf, Rg, Rh are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a -SO2-R' group wherein R' is an alkyl,

cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one

heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an OSO_2R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or an $NRaOSO_2Rb$, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a

pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Ra, Rb, Rd, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

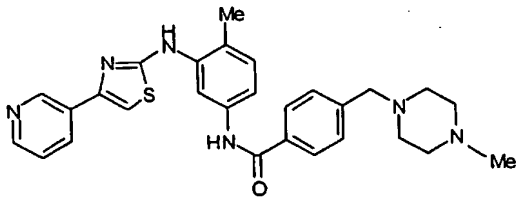
(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and

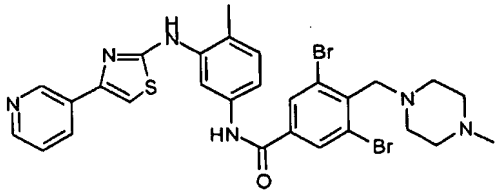
optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Examples

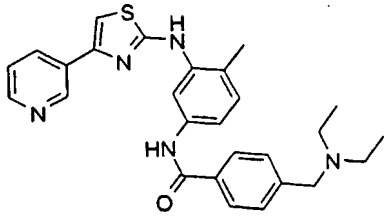
066: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



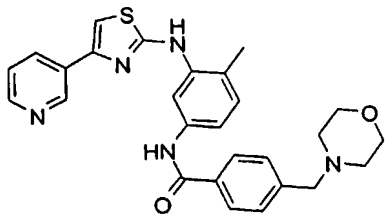
067: 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



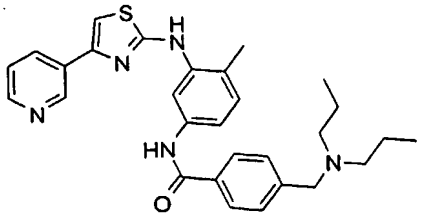
068: 4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



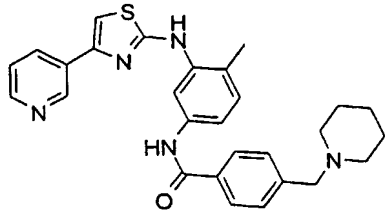
069: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide



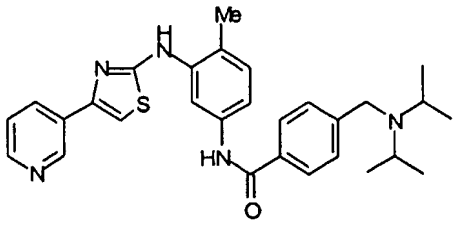
070: 4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



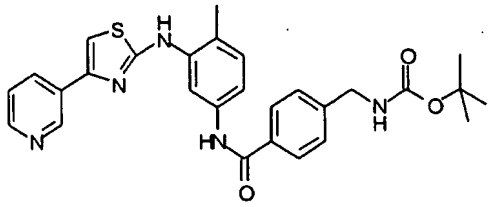
071: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



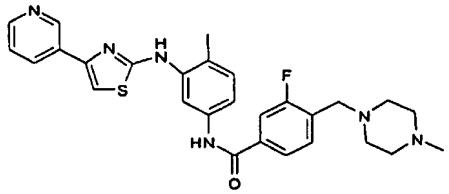
072: 4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



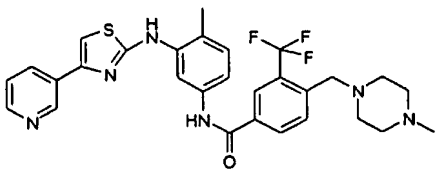
073: {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester



074: 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



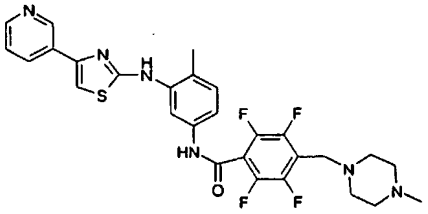
075: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-3-trifluoromethyl-benzamide



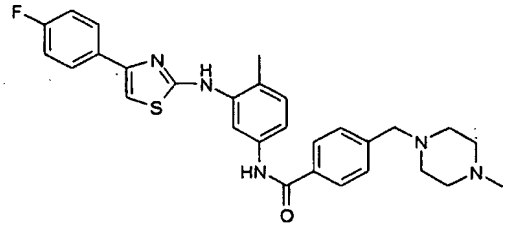
yellow crystals mp : 118-120°C

^{1}H RMN (DMSO-d^6) δ = 2.22 (s, 3H) ; 2.33 (s, 3H) ; 2.34-2.50 (m, 8H) ; 3.74 (s, 2H) ; 7.26 (d, J = 8.3Hz, 1H) ; 7.41-7.49 (m, 2H) ; 7.53 (s, 1H) ; 7.99 (d, J = 8.0 Hz, 1H) ; 8.28-8.31 (m, 2H) ; 8.38 (d, J = 7.9 Hz, 1H) ; 8.53 (dd, J = 1.3 Hz, J = 4.7 Hz, 1H) ; 8.68 (d, J = 1.9 Hz, 1H) ; 9.21 (d, J = 2.0 Hz, 1H) ; 9.53 (s, 1H) ; 10.49 (s, 1H)

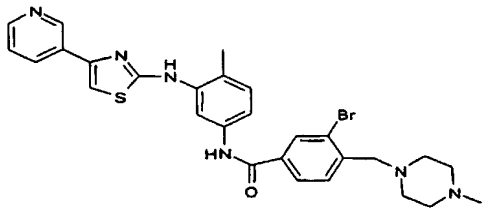
076: 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



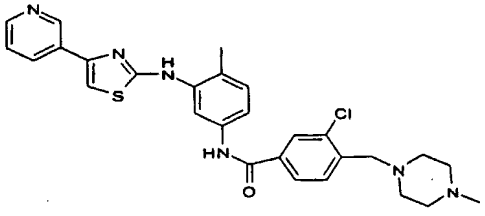
077: N-{3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



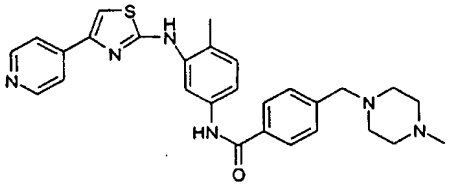
078: 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



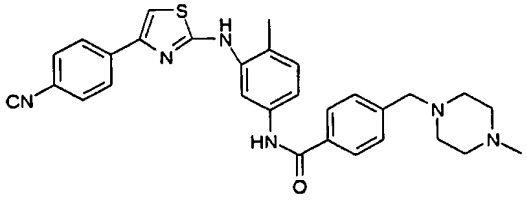
079: 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



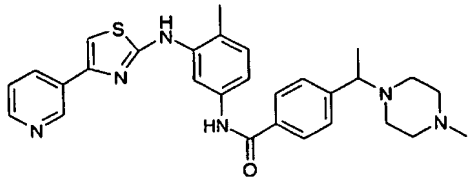
080: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide



081: N-{3-[4-(4-Cyano-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



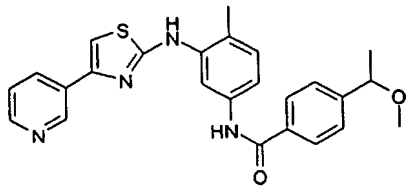
082: 4-[1-(4-Methyl-piperazin-1-yl)-ethyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



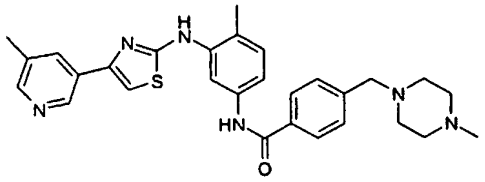
beige powder mp : 153-155°C

^{1}H RMN (DMSO-d^6) δ = 1.29 (d, J = 6.6 Hz, 3H) ; 2.15 (s, 3H) ; 2.26 (s, 3H) ; 3.15-3.25 (m, 9H) ; 7.18 (d, J = 8.4 Hz, 1H) ; 7.35-7.47 (m, 5H) ; 7.91 (d, J = 8.2 Hz, 2H) ; 8.31 (d, J = 8.0 Hz, 1H) ; 8.47 (dd, J = 1.6 Hz, J = 4.7 Hz, 1H) ; 8.60 (d, J = 2.0, 1H) ; 9.15 (d, J = 0.6, 1H) ; 9.45 (s, 1H) ; 10.18 (s, 1H)

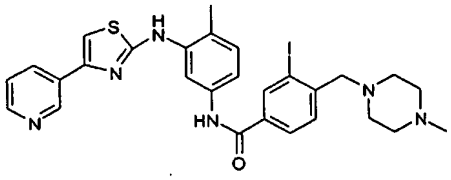
083: 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



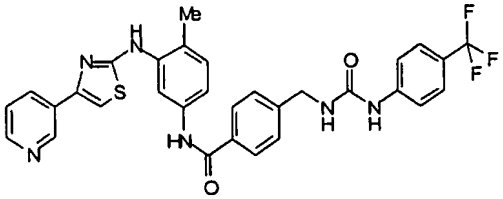
084: N-{4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



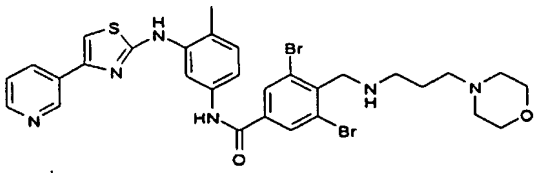
085: 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



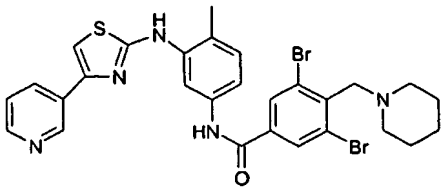
086: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide



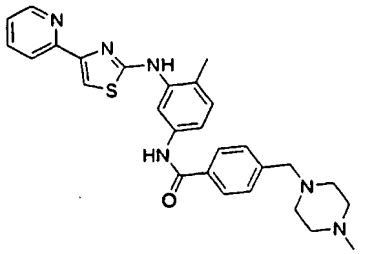
087: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[(3-morpholin-4-yl-propylamino)-methyl]-benzamide



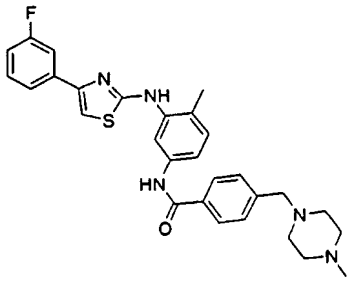
107: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



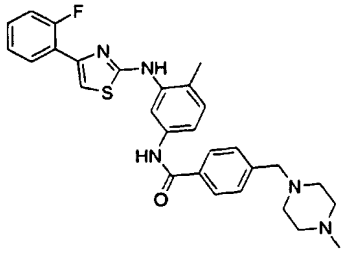
122: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



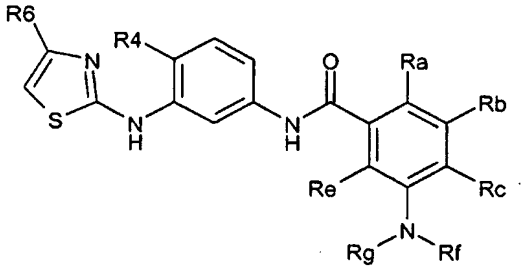
111: N-{3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



118: N-{3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamides



Among compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a -aryl-substituted group, corresponding to the 3-Disubstituted-amino-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula IV-5:



FORMULA IV-5

wherein Ra, Rb, Rc, Re, Rf, Rg are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group

optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a -SO2-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group

optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

- or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- an OSO_2R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or an $NRaOSO_2Rb$, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms atoms optionally substituted with at least one heteroatom (for example a halogen) and / or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality;

- or a -SO2-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group,

wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Ra, Rb, Rc, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

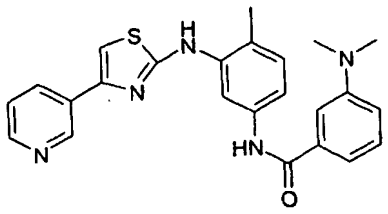
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Examples

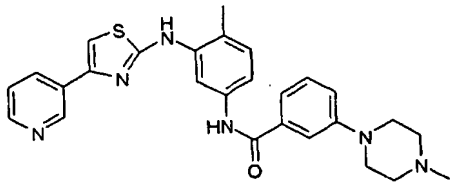
088: 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp : 197-198°C

^{1}H NMR (DMSO-d^6) : δ 2.32 (s, 3H) ; 3.03 (s, 6H) ; 6.97 (d, J = 6.4 Hz, 1H) ; 7.23-7.56 (m, 7H) ; 8.37 (d, J = 7.3 Hz, 1H) ; 8.53 (d, J = 4.7 Hz, 1H) ; 8.63 (s, 1H) ; 9.20 (s, 1H) ; 9.48 (s, 1H) ; 10.15 (s, 1H)

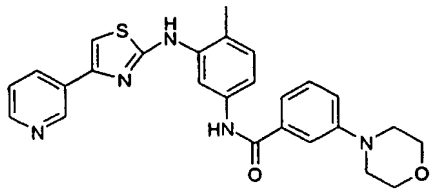
089: 3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp : 274-246°C

^{1}H RMN (DMSO-d^6) δ = 2.23 (s, 3H) ; 2.24-2.30 (m, 4H) ; 3.22-3.27 (m, 4H) ; 7.07-7.20 (m, 2H) ; 7.36-7.53 (m, 6H) ; 8.31 (d, J = 7.5 Hz, 1H) ; 8.47 (d, J = 3.7 Hz, 1H) ; 8.58 (s, 1H) ; 9.12 (d, J = 7.8 Hz, 1H) ; 9.44 (s, 1H) ; 10.12 (s, 1H)

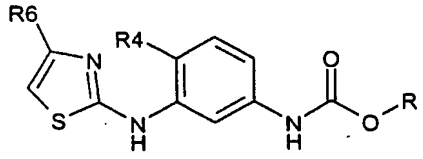
090: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-morpholin-4-yl-benzamide



beige powder mp : 247-248°C

^{1}H RMN ($CDCl_3$) δ = 1.50 (s, 3H) ; 3.15-3.18 (m, 4H) ; 3.79-3.82 (m, 3H) ; 6.85 (s, 1H) ; 7.00-7.30 (m, 7H) ; 7.41 (s, 1H) ; 7.75 (s, 1H) ; 8.08 (d, J = 7.9 Hz, 1H) ; 8.22 (d, J = 1.7 Hz, 1H) ; 8.46 (dd, J = 1.3 Hz, J = 4.7 Hz, 1H) ; 9.01 (d, J = 1.6 Hz, 1H)

Among the compounds of formula IV, the invention is particularly embodied by the compounds wherein X is a -OR group, corresponding to the family [3-(Thiazol-2-ylamino)-phenyl]-carbamate and the following formula IV-6



FORMULA IV-6

wherein R is independently chosen from an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and / or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and / or bearing a pendant basic nitrogen functionality;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

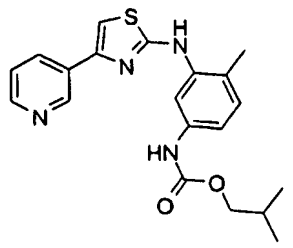
(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;s

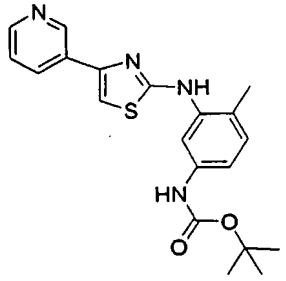
iv) H, a halogen selected from I, F, Cl or Br; NH2, NO2 or SO2-R, wherein R is a linear or branched alkyl goup containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and / or bearing a pendant basic nitrogen functionality.

Examples

097: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester

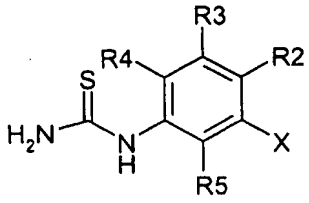


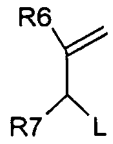
098: 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole



Process for manufacturing a compound of formula III depicted above.

This entails the condensation of a substrate of general formula 10 with a thiourea of the type 11.





11 a: X = NH-R1

10

11 b: X = NH2

11 c: X = NH-PG

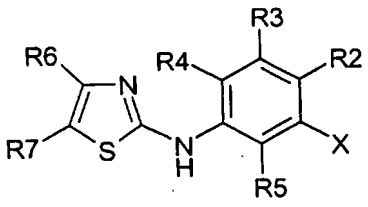
11 d: X = NO2

Substituent "L" in formula 10 is a nucleofugal leaving group in nucleophilic substitution reactions (for example, L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group).

Group R1 in formula 11a corresponds to group R1 as described in formula III.

Group "PG" in formula 11c is a suitable protecting group of a type commonly utilized by the person skilled in the art.

The reaction of 10 with 1 a-d leads to a thiozole-type product of formula **12a-d**.



12 a: X = NH-R1

12 b: X = NH2

12 c: X = NH-PG

12 d: X = NO2

Formula 12a is the same as formula I. Therefore, R1 in 12a corresponds to R1 in formula III.

Formula 12b describes a precursor to compounds of formula III which lack substituent R1. Therefore, in a second phase of the synthesis, substituent R1 is connected to the free amine group in 12b, leading to the complete structure embodied by formula III:

12b + "R1" → III

The introduction of R1, the nature of which is as described on page 3 for the general formula III, is achieved by the use of standard reactions that are well known to the person skilled in the art, such as alkylation, acylation, sulfonylation, formation of ureas, etc.

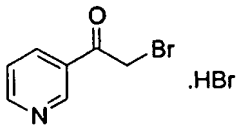
Formula 12c describes an N-protected variant of compound 12b. Group "PG" in formula 12c represents a protecting group of the type commonly utilized by the person skilled in the art. Therefore, in a second phase of the synthesis, group PG is cleaved to transform compound 12c into compound 12b. Compound 12b is subsequently advanced to structures of formula I as detailed above.

Formula 12d describes a nitro analogue of compound 12b. In a second phase of the synthesis, the nitro group of compound 12d is reduced by any of the several methods utilized by the person skilled in the art to produce the corresponding amino group, namely compound 12b. Compound 12b thus obtained is subsequently advanced to structures of formula III as detailed above.

Examples of Compound synthesis

General: All chemicals used were commercial reagent grade products. Dimethylformamide (DMF), methanol (MeOH) were of anhydrous commercial grade and were used without further purification. Dichloromethane and tetrahydrofuran (THF) were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Fluka TLC plates, which were visualized under UV light. Multiplicities in ^{1}H NMR spectra are indicated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300MHz Bruker spectrometer.

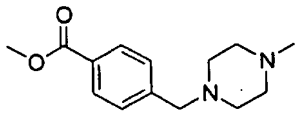
3-Bromoacetyl-pyridine, HBr salt



Dibromine (17.2g, 108 mmol) was added dropwise to a cold (0°C) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigourous stirring. The vigorously stirred mixture was warmed to 40°C for 2h and then to 75°C. After 2h at 75°C, the mixture was cooled and diluted with ether (400 mL) to precipitate the product. which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallised from methanol and ether.

IR (neat) : 3108, 2047,2982, 2559, 1709, 1603, 1221, 1035, 798 cm^{-1} - ^1H NMR (DMSO-d^6) δ = 5.09 (s, 2H, CH_2Br) ; 7.88 (m, 1H, pyridyl-H) ; 8.63 (m, 1H, pyridyl-H) ; 8.96 (m, 1H, pyridyl-H) ; 9.29 (m, 1H, pyridyl-H).

Methyl -[4-(1-N-methyl-piperazino)-methyl]-benzoate

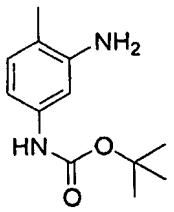


To methyl-4-formyl benzoate (4.92 g, 30 mmol) and N-methyl-piperazine (3.6 mL, 32 mmol) in acetonitrile (100 mL) was added dropwise 2.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1h. After slow addition of sodium cyanoborohydride (2 g, 32 mmol), the solution was left stirring overnight at room temperature. Water (10 mL) was then added to the mixture, which was further acidified with 1N HCl to pH=6-7. The acetonitrile was removed under reduced pressure and the residual aqueous solution was extracted with diethyl ether (4×30 mL). These extracts were discarded. The aqueous phase was then basified (pH>12) by addition of 2.5N

aqueous sodium hydroxyde solution. The crude product was extracted with ethyl acetate (4×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a slightly yellow oil which became colorless after purification by Kugelrohr distillation (190°C) in 68% yield.

IR(neat) : 3322, 2944, 2802, 1721, 1612, 1457, 1281, 1122, 1012 - ^{1}H NMR ($CDCl_3$) δ = 2.27 (s, 3H, NCH_3); 2.44 (m, 8H, 2×NCH_2CH_2N); 3.53 (s, 2H, $ArCH_2N$); 3.88 (s, 3H, OCH_3); 7.40 (d, 2H, J= 8.3 Hz,2×ArH); 7.91 (d, 2H, J= 8.3 Hz, 2×ArH) - ^{13}C NMR ($CDCl_3$) δ = 45.8 (NCH_3); 51.8 (OCH_3); 52.9 (2×CH_2N); 54.9 (2×CH_2N); 62.4 ($ArCH_2N$); 128.7 (2×ArC); 129.3 (2×ArC); 143.7(ArC); 166.7 ($ArCO_2CH_3$) - MS CI (m/z) (%) : 249 (M+1, 100%).

2-Methyl-5-tert-butoxycarbonylamino-aniline

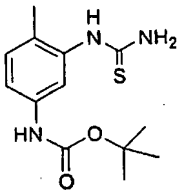


A solution of di-tert-butyldicarbonate (70 g, 320 mmol) in methanol (200 mL) was added over 2 h to a cold (–10°C) solution of 2,4-diaminotoluene (30 g, 245 mmol) and triethylamine (30 mL) in methanol (15 mL). The reaction was followed by thin layer chromatography (hexane/ethyl acetate, 3 :1) and stopped after 4h by adding 50 mL of water. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl acetate. This organic phase was washed with water (1×150 mL) and brine (2×150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting light brown solid was washed with small amounts of diethyl ether to give off-white crystals of 2-methyl-5-tert-butoxycarbonylamino-aniline in 67% yield.

IR (neat) : 3359 ; 3246 ; 2970 ; 1719 ; 1609 ; 1557 ; 1173 ; 1050 cm^{-1}- ^1H NMR ($CDCl_3$): δ = 1.50 (s, 9H, tBu); 2.10 (s, 3H, $ArCH_3$); 3.61 (br s, 2H, NH_2); 6.36 (br s, 1H, NH); 6.51 (dd, 1H, J = 7.9 Hz, 2.3 Hz, ArH); 6.92 (d, 1H, J= 7.9 Hz, ArH); 6.95 (s, 1H, ArH) - ^{13}C NMR ($CDCl_3$) δ = 16.6 ($ArCH_3$); 28.3 ($C(CH_3)_3$); 80.0 ($C(CH_3)_3$); 105.2 (ArC); 108.6 (ArC); 116.9 (ArC); 130.4 (ArC-CH_3); 137.2 (ArC-NH); 145.0 (ArC-NH_2); 152.8 (COOtBu)

MS ESI (m/z) (%) : 223 (M+1), 167 (55, 100%).

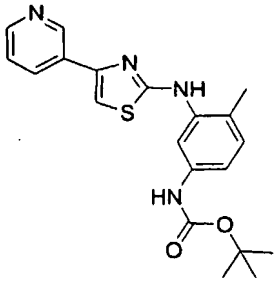
N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea



Benzoyl chloride (5.64 g, 80 mmol) was added dropwise to a well-stirred solution of ammonium thiocyanate (3.54 g, 88 mmol) in acetone (50 mL). The mixture was refluxed for 15 min, then, the hydrobromide salt of 2-methyl-5-tert-butoxycarbonylamino-aniline (8.4g, 80 mmol) was added slowly portionswise. After 1h, the reaction mixture was poured into ice-water (350 mL) and the bright yellow precipitate was isolated by filtration. This crude solid was then refluxed for 45 min in 70 mL of 2.5 N sodium hydroxide solution. The mixture was cooled down and basified with ammonium hydroxide. The precipitate of crude thiourea was recovered by filtration and dissolved in 150 mL of ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 1 :1) to afford 63 % of *N* -(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea as a white solid.

IR (neat) : 3437, 3292, 3175, 2983, 1724, 1616, 1522, 1161, 1053 cm^{-1}- ^1H NMR (DMSO-d^6) δ = 1.46 (s, 9H, tBu) ; 2.10 (s, 3H, $ArCH_3$) ; 3.60 (br s, 2H, NH_2) ; 7.10 (d, 1H, J = 8.29 Hz, ArH) ; 7.25 (d, 1H, J = 2.23 Hz, ArH) ; 7.28 (d, 1H, J = 2.63 Hz, ArH) ; 9.20 (s, 1H, ArNH) ; 9.31 (s, 1H, ArNH) - ^{13}C NMR (DMSO-d^6) δ = 25.1 ($ArCH_3$); 28.1 ($C(CH_3)_3$); 78.9 ($C(CH_3)_3$); 116.6 (ArC); 117.5 (ArC); 128.0 (ArC); 130.4 (ArC-CH_3); 136.5 (ArC-NH); 137.9 (ArC-NH); 152.7 (COOtBu); 181.4 (C=S) - MS CI(m/z) : 282 (M+1, 100%) ; 248 (33) ; 226 (55) ; 182 (99) ; 148 (133) ; 93 (188).

2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole

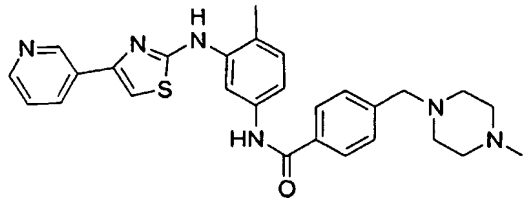


A mixture of 3-bromoacetyl-pyridine, HBr salt (0.81g, 2.85 mmol), *N* -(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea (0.8g, 2.85 mmol) and $KHCO_3$ (~0.4g) in ethanol (40 mL) was heated at 75°C for 20h. The mixture was cooled, filtered (removal of $KHCO_3$) and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (40 mL) and washed with saturated aqueous sodium hydrogen carbonate solution and with water. The organic layer was dried over Na_2SO_4 and concentrated. Colum chromatographic purification of the residue (hexane/ethyl acetate, 1 :1) gave the desired thiazole in 70% yield as an orange solid

IR(neat) : 3380, 2985, 2942, 1748, 1447, 1374, 1239, 1047, 938 - ^1H NMR ($CDCl_3$) δ = 1.53 (s, 9H, tBu) ; 2.28 (s, 3H, $ArCH_3$) ; 6.65 (s, 1H, thiazole-H) ; 6.89 (s, 1H) ; 6.99 (dd, 1H, J= 8.3 Hz, 2.3 Hz) ; 7.12 (d, 2H, J =8.3 Hz) ; 7.35 (dd, 1H, J = 2.6 Hz, 4.9 Hz) ; 8.03 (s, 1H) ; 8.19 (dt, 1H, J = 1.9 Hz, 7.9 Hz) ; 8.54 (br s, 1H, NH) ; 9.09 (s, 1H, NH)

- ^{13}C NMR ($CDCl_3$) δ = 18.02 ($ArCH_3$) ; 29.2 ($C(CH_3)_3$) ; 81.3 ($C(CH_3)_3$) ; 104.2 (thiazole-C) ; 111.6 ; 115.2 ; 123.9 ; 124.3 ; 131.4 ; 132.1 ; 134.4 ; 139.5 ; 148.2 ; 149.1 ; 149.3 ; 153.6 ; 167.3 (C=O) - MS CI (m/z) (%) : 383 (M+1, 100%) ; 339 (43) ; 327 (55) ; 309 (73) ; 283 (99) ; 71 (311).

2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole

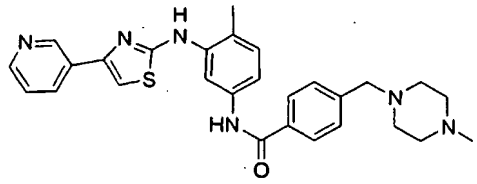


2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole (0.40g, 1.2 mmol) was dissolved in 10 mL of 20% TFA/CH_2Cl_2. The solution was stirred at room temperature for 2h, then it was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 1N sodium hydroxide solution, dried over $MgSO_4$, and concentrated to afford **2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole** as a yellow-orange solid in 95% yield. This crude product was used directly in the next step.

A 2M solution of trimethyl aluminium in toluene (2.75 mL) was added dropwise to a cold (0° C) solution of 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole (0.42 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) under argon atmosphere. The mixture was warmed to room temperature and stirred at room temperature for 30 min. A solution of methyl-4-(1-N-methyl-piperazino)-methyl benzoate (0.45 g, 1.8 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 5h. The mixture was cooled to 0°C and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (3 mL). The mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine

(3×20 mL) and dried over anhydrous $MgSO_4$. (2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole) is obtained in 72% after purification by column chromatography (dichloromethane/ methanol, 3 :1)

IR (neat) : 3318, 2926, 1647, 1610, 1535, 1492, 1282, 1207, 1160, 1011, 843 - ^{1}H NMR ($CDCl_3$) δ = 2.31 (br s, 6H, $ArCH_3$+NCH_3) ; 2.50 (br s, 8H, 2×NCH_2CH_2N) ; 3.56 (s, 2H, $ArCH_2N$) ; 6.89 (s, 1H, thiazoleH) ; 7.21-7.38 (m, 4H); 7.45 (m, 2H) ; 7.85 (d, 2H, J = 8.3Hz) ; 8.03 (s, 1H) ; 8.13 (s, 1H) ; 8.27 (s, 1H) ; 8.52 (br s, 1H) ; 9.09 (s, 1H, NH) - ^{13}C NMR ($CDCl_3$) δ = 17.8 ($ArCH_3$) ; 46.2 (NCH_3) ; 53.3 (NCH_2) ; 55.3 (NCH_2) ; 62.8 ($ArCH_2N$) ; 99.9 (thiazole-C) ; 112.5 ; 123.9 ; 125.2 ; 127.5 ; 129.6 ; 131.6 ; 133.7 ; 134.0 ; 137.6 ; 139.3 ; 142.9 ; 148.8 ; 149.1 ; 166.2 (C=O) ; 166.7 (thiazoleC-NH) - MS CI (m/z) (%) : 499 (M+H, 100%) ; 455 (43) ; 430 (68) ; 401 (97) ; 374 (124) ; 309 (189) ; 283 (215) ; 235 (263) ; 121 (377) ; 99 (399).



The expression "cerebral ischemia" as referred herein include but are not limited to hypoxic-ischemic encephalopathy induced by stroke, traumatic brain injury such as cerebral edema and embolic or thromboembolic occlusions of cerebral arteries, and ischemic insults following reperfusion.

More particularly, the method according to the invention is useful for preventing the onset or development of nerve cells damages few hours following either the cause of the ischemia or before, during and after reperfusion.

In a further embodiment, c-kit inhibitors as mentioned above are inhibitors of activated c-kit. In frame with the invention, the expression "activated c-kit" means a constitutively activated-mutant c-kit including at least one mutation selected from point mutations, deletions, insertions, but also modifications and alterations of the natural c-kit sequence (SEQ ID N°1). Such mutations, deletions, insertions, modifications and alterations can occur in the transphosphorylase domain, in the juxtamembrane domain as well as in any domain directly or indirectly responsible for c-kit activity. The expression "activated c-kit" also means herein SCF-activated c-kit. Preferred and optimal SCF concentrations for activating c-kit are comprised between 5.10^{-7} M and 5.10^{-6} M, preferably around 2.10^{-6} M. In a preferred embodiment, the activated-mutant c-kit in step a) has at least one mutation proximal to Y823, more particularly between amino acids 800 to 850 of SEQ ID No1 involved in c-kit autophosphorylation, notably the D816V, D816Y, D816F and D820G mutants. In another preferred embodiment, the activated-mutant c-kit in step a) has a deletion in the juxtamembrane domain of c-kit. Such a deletion is for example between codon 573 and 579 called c-kit d(573-579). The point mutation V559G proximal to the juxtamembrane domain c-kit is also of interest.

In this regard, the invention contemplates a method for treating cerebral ischemia as defined above comprising administering to a human in need of such treatment a compound that is a selective, potent and non toxic inhibitor of activated c-kit obtainable by a screening method which comprises :

a) bringing into contact (i) activated c-kit and (ii) at least one compound to be tested; under conditions allowing the components (i) and (ii) to form a complex,

b) selecting compounds that inhibit activated c-kit,

c) testing and selecting a subset of compounds identified in step b), which are unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

This screening method can further comprise the step consisting of testing and selecting a subset of compounds identified in step b) that are inhibitors of mutant activated c-kit (for example in the transphosphorylase domain), which are also capable of inhibiting SCF-activated c-kit wild.
Alternatively, in step a) activated c-kit is SCF-activated c-kit wild.

A best mode for practicing this method consists of testing putative inhibitors at a concentration above 10 μM in step a). Relevant concentrations are for example 10, 15, 20, 25, 30, 35 or 40 μM.

In step c), IL-3 is preferably present in the culture media of IL-3 dependent cells at a concentration comprised between 0.5 and 10 ng/ml, preferably between 1 to 5 ng/ml.

Examples of IL-3 dependent cells include but are not limited to :
- cell lines naturally expressing and depending on c-kit for growth and survival. Among such cells, human mast cell lines can be established using the following procedures : normal human mast cells can be infected by retroviral vectors containing sequences coding for a mutant c-kit comprising the c-kit signal peptide and a TAG sequence allowing to differentiate mutant c-kits from c-kit wild expressed in hematopoetic cells by means of antibodies.

This technique is advantageous because it does not induce cellular mortality and the genetic transfer is stable and gives satisfactory yields (around 20 %). Pure normal human mast cells can be routinely obtained by culturing precursor cells originating from blood obtained from human umbilical vein. In this regard, heparinated blood from umbilical

vein is centrifuged on a Ficoll gradient so as to isolate mononucleated cells from other blood components. CD34+ precursor cells are then purified from the isolated cells mentioned above using the immunomagnetic selection system MACS (Miltenyi biotech). CD34+ cells are then cultured at 37°C in 5 % CO_2 atmosphere at a concentration of 10^5 cells per ml in the medium MCCM (α-MEM supplemented with L-glutamine, penicillin, streptomycin, 5 10^{-5} M β-mercaptoethanol, 20 % veal fœtal serum, 1 % bovine albumin serum and 100 ng/ml recombinant human SCF. The medium is changed every 5 to 7 days. The percentage of mast cells present in the culture is assessed each week, using May-Grünwal Giemsa or Toluidine blue coloration. Anti-tryptase antibodies can also be used to detect mast cells in culture. After 10 weeks of culture, a pure cellular population of mast cells (> 98 %) is obtained.

It is possible using standard procedures to prepare vectors expressing c-kit for transfecting the cell lines established as mentioned above. The cDNA of human c-kit has been described in Yarden et al., (1987) EMBO J.6 (11), 3341-3351. The coding part of c-kit (3000 bp) can be amplified by PCR and cloned, using the following oligonucleotides :

- 5'AAGAAGAGATGGTACCTCGAGGGGTGACCC3' (SEQ ID No 2) sens
- 5'CTGCTTCGCGGCCGCGTTAACTCTTCTCAACCA3' (SEQ ID No 3) antisens

The PCR products, digested with Not1 and Xho1, has been inserted using T4 ligase in the pFlag-CMV vector (SIGMA), which vector is digested with Not1 and Xho1 and dephosphorylated using CIP (Biolabs). The pFlag-CMV-c-kit is used to transform bacterial clone XL1-blue. The transformation of clones is verified using the following primers :

- 5'AGCTCGTTTAGTGAACCGTC3' (SEQ ID No 4) sens,

- 5'GTCAGACAAAATGATGCAAC3' (SEQ ID No 5) antisens.

Directed mutagenesis is performed using relevant cassettes is performed with routine and common procedure known in the art..

The vector Migr-1 (ABC) can be used as a basis for constructing retroviral vectors used for transfecting mature mast cells. This vector is advantageous because it contains the sequence coding for GFP at the 3' and of an IRES. These features allow to select cells infected by the retrovirus using direct analysis with a fluorocytometer. As mentioned above, the N-terminal sequence of c-kit c-DNA can be modified so as to introduce a Flag sequence that will be useful to discriminating heterogeneous from endogenous c-kit.

Other IL-3 dependent cell lines that can be used include but are not limited to:

- BaF3 mouse cells expressing wild-type or mutated form of c-kit (in the juxtamembrane and in the catalytic sites) are described in Kitayama et al, (1996), Blood 88, 995-1004 and Tsujimura et al, (1999), Blood 93, 1319-1329.
- IC-2 mouse cells expressing either c-kit^{WT} or c-kit^{D814Y} are presented in Piao et al, (1996), Proc. Natl. Acad. Sci. USA 93, 14665-14669.

IL-3 independent cell lines are :

- HMC-1, a factor-independent cell line derived from a patient with mast cell leukemia, expresses a juxtamembrane mutant c-kit polypeptide that has constitutive kinase activity (Furitsu T et al, J Clin Invest. 1993;92:1736-1744 ; Butterfield et al, Establishment of an immature mast cell line from a patient with mast cell leukemia. Leuk Res. 1988;12:345-355 and Nagata et al, Proc Natl Acad Sci U S A. 1995;92:10560-10564).
- P815 cell line (mastocytoma naturally expressing c-kit mutation at the 814 position) has been described in Tsujimura et al, (1994), Blood 83, 2619-2626.

The extent to which component (ii) inhibits activated c-kit can be measured *in vitro* or *in vivo*. In case it is measured *in vivo*, cell lines expressing an activated-mutant c-kit, which has at least one mutation proximal to Y823, more particularly between amino acids 800 to 850 of SEQ ID No1 involved in c-kit autophosphorylation, notably the D816V, D816Y, D816F and D820G mutants, are preferred.
Example of cell lines expressing an activated-mutant c-kit are as mentioned above.

In another preferred embodiment, the method further comprises the step consisting of testing and selecting compounds capable of inhibiting c-kit wild at concentration below 1 μM. This can be measured *in vitro* or *in vivo*.

Therefore, compounds are identified and selected according to the method described above are potent, selective and non-toxic c-kit wild inhibitors.

Alternatively, the screening method as defined above can be practiced *in vitro*. In this regard, the inhibition of mutant-activated c-kit and/or c-kit wild can be measured using standard biochemical techniques such as immunoprecipitation and western blot. Preferably, the amount of c-kit phosphorylation is measured.

In a still further embodiment, the invention contemplates a method for treating cerebral ischemia as depicted above wherein the screening comprises :
a) performing a proliferation assay with cells expressing a mutant c-kit (for example in the transphosphorylase domain), which mutant is a permanent activated c-kit, with a plurality of test compounds to identify a subset of candidate compounds targeting activated c-kit, each having an IC50 < 10 μM, by measuring the extent of cell death,

b) performing a proliferation assay with cells expressing c-kit wild said subset of candidate compounds identified in step (a), said cells being IL-3 dependent cells cultured in presence of IL-3, to identify a subset of candidate compounds targeting specifically c-kit,

c) performing a proliferation assay with cells expressing c-kit, with the subset of compounds identified in step b) and selecting a subset of candidate compounds targeting c-kit wild, each having an IC50 < 10 μM, preferably an IC50 < 1 μM, by measuring the extent of cell death.

Here, the extent of cell death can be measured by 3H thymidine incorporation, the trypan blue exclusion method or flow cytometry with propidium iodide. These are common techniques routinely practiced in the art.

The method according to the invention includes preventing, delaying the onset and/or treating cerebral ischemia and associated damages in humans.

In the method defined above, any compound capable of depleting mast cells can be used. Such compounds can belong to, as explicated above, tyrosine kinase inhibitors, such as c-kit inhibitors, but are not limited to any particular family so long as said compound shows capabilities to deplete mast cells. Depletion of mast cells can be evaluated using for example one of the mast cell lines depicted above using routine procedure.

Best compounds are compounds exhibiting the greatest selectivity.

Control cell lines include other hematopoeitic cells that are not mast cells or related cells or cell lines. These control cell lines include SCF independent expanded human CD34+ normal cells. These control cells also include but are not limited to the human T lymphocyte Jurkat cell line (ATCC N° TIB-152 and mutant cell lines derived thereof), the human B lymphocyte Daudi or Raji cell line (ATCC N° CCL-213 and CCL-86 respectively), the human monocytic U 937 cell line (ATCC N° CRL-1593.2) and the

human HL-60 cell line (ATCC N° CCL-240) and mutant cell lines derived thereof CRL-2258 and CRL-2392).

Such compounds can be selected with a method for identifying compounds capable of depleting mast cells, said compound being non-toxic for cell types other than mast cells, comprising the step consisting of :

a) culturing mast cells in vitro in a culture medium suitable for mast cells,

b) adding to said culture medium at least one compound to be tested and incubating said cells for a prolonged period of time,

c) selecting compounds that promote mast cells death,

d) identifying a subset of compounds selected in step c) that are unable to promote death of cells selected from the above mentioned control cell lines.

Therefore, the invention embraces the use of the compounds defined above to manufacture a medicament for treating cerebral ischemia such as hypoxic-ischemic encephalopathy induced by stroke, traumatic brain injury such as cerebral edema and embolic or thromboembolic occlusions of cerebral arteries, and ischemic insults following reperfusion.

More particularly, the above compounds are useful for preventing the onset or development of nerve cells damages few hours following either the cause of the ischemia or before, during and after reperfusion.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

More particularly, the invention relates to a pharmaceutical composition intended for oral administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein compounds for depleting mast cells, such as tyrosine kinase inhibitors and c-kit inhibitors, are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. As

mentioned above, a tyrosine kinase inhibitor and more particularly a c-kit inhibitor according to the invention is unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

Example 1 : in vitro TK inhibition assays

- **Procedure**

Experiments were performed using purified intracellular domain of c-kit expressed in baculovirus. Estimation of the kinase activity was assessed by the phosphorylation of tyrosine containing target peptide estimated by established ELISA assay.

- **Experimental results on tested compounds**

Result in Table 2 shows the potent inhibitory action of the catalytic activity of c-kit with an IC50 <10 μM. Further experiments (not shown) indicates that at least one compound acts as perfect competitive inhibitors of ATP.

Table 2:

Compounds	In vitro Inhibition assay results
	c-kit IC50 (μM)
066; 074; 078; 084; 012; 016; 073; 021; 088; 023; 025; 047; 048; 055; 049; 026; 087; 075; 089; 051; 082; 090; 060; 085; 052; 053; 096	<10μM

Example 2 : ex vivo TK inhibition assays

- **Procedures**
  - **C-Kit assay**

Proliferation assays

Cells were washed two times in PBS before plating at 5 x 10_4 cells per well of 96-well plates in triplicate and stimulated either with hematopoietic growth factors (HGF) or

without. After 2 days of culture, 37 Bq (1.78 Tbq/mmol) of [$_3$H] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [$_3$H] thymidine incorporation was measured in a scintillation counter. For proliferation assay, all drugs were prepared as 20mM stock solutions in DMSO and conserved at -80°C. Fresh dilutions in PBS were made before each experiment. DMSO dissolved drugs were added at the beginning of the culture. Control cultures were done with corresponding DMSO dilutions. Results are represented in percentage by taking the proliferation without inhibitor as 100%.

Cells

Ba/F3 murine kit and human kit are derived from the murine IL-3 dependent Ba/F3 proB lymphoid cells. The human leukaemic MC line HMC-1 expresses mutations JM-V560G;

Immunoprecipitation assays and western blotting analysis

For each assay, 5.10$_6$ Ba/F3 cells and Ba/F3-derived cells with various c-kit mutations were lysed and immunoprecipitated as described (Beslu *et al.*, 1996), excepted that cells were stimulated with 250 ng / ml of rmKL. Cell lysates were immunoprecipitated with a rabbit immunserum anti murine KIT, directed against the KIT cytoplasmic domain (Rottapel *et al.*, 1991). Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the rabbit immunserum anti-murine KIT or with different antibodies (described in antibodies paragraph). The membrane was then incubated either with HRP-conjugated goat anti mouse IgG antibody or with HRP-conjugated goat anti rabbit IgG antibody (Immunotech), Proteins of interest were then visualized by incubation with ECL reagent (Amersham).

- **Experimental results**

The experimental results for various compounds according to the invention using above-described protocols are set forth at Table 3:

Table 3:

Target	IC50 (μM)	Compounds
c-Kit WT	IC50 < 10 μM	002; 005; 006; 007; 008; 009; 010; 012; 017; 019; 020; 021; 023; 024; 025; 026; 028; 029; 030; 032; 042; 043; 045; 047; 048; 049; 050; 051; 052; 053; 054; 055; 056; 057; 059; 060; 061; 062; 063; 064; 065; 066; 067; 072; 073; 074; 075; 077; 078; 079; 080; 081; 082; 083; 084; 085; 086; 087; 088; 089; 090; 092; 093; 094; 095; 096; 097; 106; 105; 104; 103;128; 129; 130; 131; 117; 110; 116; 124; 108; 122; 111; 113; 118; 107;

Example 3 : Evaluation of c-kit inhibitors AB-1001 and AB-III of formula III.

The purpose of these studies was to assess the AB of tyrosine kinase and c-kit inhibitors as described above in transitory ischemia mouse model.

3.1 Materials and Method

The model consists of occluding the middle cerebral artery (MCA) in male Swiss mouse (weight from 22 to 26 g) anesthetized with IP injection of 400 mg/kg chloral hydrate. The animal is placed under thermostated blanket during surgery. Common carotid artery (CCA), external carotid artery (ECA), and left internal carotid artery (ICA) are isolated. ECA and CCA are ligated with a 4/0 silk thread (Ethicon). The ICA is transiently occluded with a microclamp to allow CCA incision and introduction of a 13 to 15 mm polyamine monothread Ethilon 6/0 (Ethicon). The thread is ligated on the CCA. The thread is withdrawn after 15 min.

Results

Neurological deficit is evaluated by the Grip Test (Couturier JY et al, Exp Neurol. 2003 Dec;184(2):973-80). The animal is brought near the grip until it grasps it and then is released. The time in seconds during which the mice grasps the rod is determined. Maximum observation is 30 s (see Table III) below.

Table III : Effect of AB-1001 and AB-III on the grip score evaluated 24h after transient cerebral ischemia.

Mice	Non operated	Vehicle	AB-1001 25 mg/kg	AB-1001 50 mg/kg	AB-III 50 mg/kg
1	30	10	3	5	30
2	30	0	30	30	20
3	30	30	18	6	30
4	30	30	30	30	30
5	30	15	12	12	2
6	30	0	30	30	30
Mean	**30 s**	**14 s ***	**21 s**	**19 s**	**24 s**
s.e.m	0	6	5	5	5

ANOVA: F = 4.435, P = 0.004

PLSD Fisher's test*: P = 0.012 versus non-operated mice; P = 0.077 versus vehicle treated ischemic mice.

A1001 and AB-III were administered at 25 or 50 mg/kg, the vehicle were given intraperitoneally before the onset of ischemia and repeated 7h 30 after.

Table IV: Effect of AB1001 and AB-III on the string score evaluated 24 h after transient focal cerebral ischemia.

Mice	Non operated	Vehicle	AB-1001 25 mg/kg	AB-1001 50 mg/kg	AB-III 50 mg/kg
1	4	0	0	0	4
2	4	0	4	4	0
3	5	4	0	0	4
4	5	4	3	4	1
5	4	0	0	0	0
6	5	0	3	4	2
Mean	**4.5**	**1.3 ****	**1.7**	**2.0**	**1.8**
s.e.m	0.2	0.8	0.9	5	0.7

ANOVA: F = 4.360, P = 0.004

PLSD Fisher's test**: P = 0.003 versus non-operated mice

A1001 and AB-III were administered at 25 or 50 mg/kg, the vehicle were given intraperitoneally 30 minutes before the onset of ischemia and repeated 7h 30 after.

Table V: Effect of AB1001 and AB-III on the Hall score evaluated 24h after transient focal cerebral ischemia.

Mice	Non operated	Vehicle	AB-1001 25 mg/kg	AB-1001 50 mg/kg	AB-III 50 mg/kg
1	5	3	2	2	5
2	5	2	5	5	4
3	6	5	3	2	5
4	6	5	5	5	4
5	5	4	4	3	2

6	6	2	5	5	5
Mean	**5.5**	**3.5****	**4.0**	**3.7**	**4.2**
s.e.m	0.2	0.6	0.5	0.6	0.5

ANOVA: F = 4.480, P = 0.001

PLSD Fisher's test**: P = 0.005 versus non-operated mice ; P = 0.037 versus vehicle treated ischemic mice

A1001 and AB-III were administered at 25 or 50 mg/kg, the vehicle were given intraperitoneally 30 minutes before the onset of ischemia and repeated 7h 30 after.

Table VI: Effect of AB1001 and AB-III on the body temperature evaluated 24h after transient focal cerebral ischemia.

Mice	Vehicle	AB-1001 25 mg/kg	AB-1001 50 mg/kg	AB-III 50 mg/kg
1	36.5	35.5	36.2	37.0
2	37.1	37.0	37.5	37.5
3	36.5	37.0	36.5	37.0
4	37.5	37.0	37.5	37.5
5	37	37.0	37.5	37.5
6	37.5	37.4	36.5	37.5
Mean °C	**37.0**	**36.8°C**	**37.0**	**37.3°C**
s.e.m	0.2	0.3	0.3	0.1

ANOVA: F = 19.830, P < 0.001

A1001 and AB-III were administered at 25 or 50 mg/kg, the vehicle were given intraperitoneally 30 minutes before the onset of ischemia and repeated 7h 30 after.

Table VII: Effect of AB1001 and AB-III on the loss of weight evaluated 24h after transient focal cerebral ischemia.

Mice	Vehicle	AB-1001 25 mg/kg	AB-1001 50 mg/kg	AB-III 50 mg/kg
1	20%	19%	21%	13%
2	21%	16%	12%	22%
3	21%	23%	19%	20%
4	23%	22%	17%	22%
5	17%	19%	24%	28%
6	20%	22%	17%	21%
Mean °C	**20%**	**20%**	**18%**	**21%**
s.e.m	1%	1%	2%	2%

ANOVA: $F = 8.834$, $P < 0.001$

A1001 and AB-III were administered at 25 or 50 mg/kg, the vehicle were given intraperitoneally 30 minutes before the onset of ischemia and repeated 7h 30 after.